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(71) Applicant: **ALDER BIOPHARMACEUTICALS, INC.** [US/US]; 11804 North Creek Parkway South, Bothell, Washington 98011 (US).

(72) Inventors: **FELDHAUS, Andrew, Lawrence**; 6903 189th Place, SW, Lynnwood, Washington 98036 (US). **GARCIA-MARTINEZ, Leon**; 4926 214th Street, SE, Woodinville, Washington 98072 (US). **DUTZAR, Benjamin, H.**; 3124A Franklin Avenue, E., Seattle, Washington 98102 (US). **ALLISON, Daniel, S.**; 19223 55th Avenue, NE, Lake Forest Park, Washington 98155 (US). **ANDERSON, Katie, Olson**; 13235 86th Place, NE, Kirkland, Washington 98034 (US). **OJALA, Ethan, Wayne**; 14310 Nevers Road, Snohomish, Washington 98290 (US). **FAN, Pei**; 1905 243rd Street, SW, Bothell, Washington 98021 (US). **KARASEK, Charlie**; 1221 Minor Avenue, Apt. 709, Seattle, Washington 98101 (US). **MULLIGAN, Jenny**; 19512 53rd Avenue, NE, Lake Forest Park, Washington 98155 (US). **SCALLEY-KIM, Michelle**; 3002 19th Aveue, S, Seattle, Washington 98144 (US). **STEWART, Erica**; 103 NE 147th Street, Shoreline, Washington 98155 (US). **SMITH, Jeffrey, T. L.**; 10270 NE 12th Street, Apt. F307, Bellevue, Washington 98004 (US). **LATHAM, John, A.**; 2409 10th Avenue, W, Seattle, Washington 98119 (US).

(74) Agents: **TESKIN, Robin, L.** et al.; Leclair Ryan, P.C., Intellectual Property Department, 2318 Mill Road, Suite 1100, Alexandria, Virginia 22314 (US).

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[Continued on next page]

(54) Title: ANTI-ACTH ANTIBODIES AND USE THEREOF

Figure 1A
Antibody Heavy chain Protein features

Sequence Name	FR1	CDR1	FR2	CDR2
Ab1	QSVKESGGRLVTPGTPLTLTCTVSGFSLS	NYDMI	WVRQAPGKGLESIG	MIYDEGDTYYASWAKG
Ab2	QSVEESGGRLVTPGTPLTLTCTVSGFSLS	KYDMI	WVRQAPGKGLESIG	IIYDDGDTYYASWAKG
Ab3	QSLEESGGRLVTPGTPLTLTCTVSGSSLS	NFDMI	WVKQAPGKGLESIG	IIYDFGSTYYASWAKG
Ab4	QSVEESGGRLVTPGTPLTLTYTVSGFSLS	KHDMI	WVRQAPGKGLESIG	IIYDDGDTYYANWAKG
Ab5	QSVEESGGRLVTPGTPLTLTCTVSGFSLS	SYAMS	WVRQAPGEGLEWIG	IISDSGSTYYASWAKG
Ab6	QSVEESGGRLVTPGTPLTLTCTVSGFSLT	DYAMS	WVRQAPGEGLEWIG	IISDSGSTYYASWAKG
Ab7	QSVEESGGRLVTPGTPLTLTCTVSGFSLS	SYAMS	WVRQAPGEGLEWIG	IISDSGSTYYASWAKG
Ab9	QSVEESGGRLVTPGTPLTLTCTVSGFSLN	SYAMS	WVRQAPGEGLEWIG	IISDSGRTYYASWAKG
Ab10	QSVEESGGRLVTPGTPLTLTCTVSGFSLS	SADMI	WVRQAPGKGLESIG	MIYDDGDTYYATWAKG
Ab11	QSLEESGGRLVTPGTSLTLTCTASGFSLS	AYDIL	WVRQAPGKGLESIG	MMYDDGDTYYATWAKG
Ab12	QSVKESGGRLVTPGTPLTLTCTVSGSSLS	DYDMI	WVRQAPGKGLESIG	IIYDDGDTYYATWAKG
Ab1.H	EVQLVESGGGLVQPGGSLRLSCAASGFTVS	NYDMI	WVRQAPGKGLESIG	MIYDDGDTYYASSAKG
Ab2.H	EVQLVESGGGLVQPGGSLRLSCAASGFTVS	KYDMI	WVRQAPGKGLESIG	IIYDDGDTYYASSAKG
Ab3.H	EVQLVESGGGLVQPGGSLRLSCAASGSSLS	NFDMI	WVRQAPGKGLESIG	IIYDFGSTYYASSAKG
Ab4.H	EVQLVESGGGLVQPGGSLRLSCAASGFTVS	KHDMI	WVRQAPGKGLESIG	IIYDDGDTYYANSAKG
Ab6.H	EVQLVESGGGLVQPGGSLRLSCAASGFSLT	DYAMS	WVRQAPGKGLEWIG	IISDSGSTYYASSAKG
Ab7.H	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	SYAMS	WVRQAPGKGLEWIG	IISDSGSTYYASSAKG
Ab7A.H	EVQLVESGGGLVQPGGSLRLSCAASGFSLS	SYAMS	WVRQAPGKGLEWIG	IISDSGSTYYASSAKG
Ab10.H	EVQLVESGGGLVQPGGSLRLSCAASGFTVS	SADMI	WVRQAPGKGLESIG	MIYDDGDTYYATSAKG
Ab11.H	EVQLVESGGGLVQPGGSLRLSCAASGFTVS	AYDIL	WVRQAPGKGLESIG	MMYDDGDTYYATSAKG
Ab11A.H	EVQLVESGGGLVQPGGSLRLSCAASGFTVS	AYDIL	WVRQAPGKGLESIG	MMYDDGDTYYATSAKG
Ab12.H	EVQLVESGGGLVQPGGSLRLSCAASGSSLS	DYDMI	WVRQAPGKGLESIG	IIYDDGDTYYATSAKG

(57) Abstract: The present invention is directed to antibodies and fragments thereof having binding specificity for ACTH. Another embodiment of this invention relates to the antibodies binding fragments thereof described herein, comprising the sequences of the VH, VL and/or CDR polypeptides described herein, and the polynucleotides encoding them. The invention also contemplates conjugates of anti-ACTH antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties. The invention further contemplates methods of making said anti-ACTH antibodies and binding fragments thereof. Embodiments of the invention also pertain to the use of anti-ACTH antibodies and binding fragments thereof for the diagnosis, assessment, prevention and treatment of diseases and disorders associated with ACTH, such as Cushing's Disease, Cushing's Syndrome, Parkinson's disease, obesity, diabetes, sleep disorders depression, anxiety disorders, cancer, muscle atrophy, hypertension, hyperinsulinemia, cognitive dysfunction, Alzheimer's disease, galactorrhea, stress related conditions, cardiac conditions, metabolic syndrome, hyperaldosteronism, Conn's syndrome and familial hyperaldosteronism.

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ANTI-ACTH ANTIBODIES AND USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 62/094,763, filed December 19, 2014 (Atty. Docket No. 43257.5403), U.S. Provisional Application Ser. No. 61/948,922, filed March 6, 2014 (Atty. Docket No. 43257.5401), U.S. Provisional Application Ser. No. 61/948,920, filed March 6, 2014 (Atty. Docket No. 43257.5400), U.S. Provisional Application Ser. No. 61/942,416, filed Feb. 20, 2014 (Atty. Docket No. 43257.5401), and U.S. Provisional Application Ser. No. 61/942,280, filed February 20, 2014 (Atty. Docket No. 43257.5400), each entitled "ANTI-ACTH ANTIBODIES AND USE THEREOF" each of which is hereby incorporated by reference in its entirety.

SEQUENCE DISCLOSURE

[0002] The instant application contains a Sequence Listing, which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. The ASCII copy, created on February 17, 2015, is named "43257o5413.txt" and is 541,162 bytes in size.

FIELD

[0003] This invention pertains to novel antibodies and antibody fragments, preferably chimeric, humanized or human antibodies and fragments thereof that specifically bind to human adrenocorticotrophic hormone (hereinafter "ACTH") and compositions containing these anti-ACTH antibodies and anti-ACTH antibody fragments. Preferably, such anti-ACTH antibodies or antibody fragments (i) will not substantially interact with (bind) a polypeptide consisting of the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, and/or (ii) the 22 C-terminal amino acid residues of ACTH ($ACTH_{18-39}$) (Corticotropin-Like Intermediate Peptide or CLIP). In addition, the invention relates to nucleic acids encoding said anti-ACTH antibodies and anti-ACTH antibody fragments. Further, the invention pertains to the use of said nucleic acids to express said antibodies and antibody fragments in desired host cells. Also, the invention pertains to anti-idiotypic antibodies produced against any of such antibodies.

[0004] The invention further relates to therapeutic and diagnostic uses of anti-ACTH antibodies and antibody fragments, preferably chimeric, humanized or human antibodies and antibody fragments that specifically bind to ACTH that antagonize one or more ACTH-related activities in the treatment or prophylaxis of diseases wherein the suppression of ACTH-related activities and/or the reduction of steroid, e.g., cortisol, corticosterone and/or aldosterone, levels are therapeutically or prophylactically desirable, including Cushing's disease, Cushing's Syndrome, hyperaldosteronism including primary hyperaldosteronism (such as Conn's syndrome) secondary hyperaldosteronism, and familial

hyperaldosteronism, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), obesity, diabetes, anxiety disorders, cognitive dysfunction, Alzheimer's disease, and other conditions disclosed herein. Preferably such antibodies or antibody fragments will not substantially interact with (bind) a polypeptide consisting of the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, or (ii) the 22 C-terminal amino acid residues of ACTH ($ACTH_{18-39}$) (CLIP).

BACKGROUND

[0005] Adrenocorticotropin (ACTH), a 39 amino acid peptide, is produced by cleavage of a large precursor molecule, pro-opiomelanocortin (POMC). Post-translational enzymatic processing of POMC yields other biologically active peptides (e.g., corticotropin-like intermediate peptide (CLIP), melanocyte-stimulating hormone (MSH), and lipotrophin (LPH)) in addition to ACTH as a result of tissue-specific processing of POMC. See Bicknell, *J. Neuroendocrinology* 20: 692-99 (2008).

[0006] The *POMC* gene has been remarkably conserved throughout evolution. A variety of organisms have a single functional copy of the gene with the same overall gene structure. The *POMC* gene is predominantly expressed in the anterior and intermediate lobes of the pituitary, and it is generally accepted that the majority of POMC peptides found in the circulation are derived from the pituitary, whereas POMC peptides produced in extra-pituitary tissues (e.g., brain, lymphocytes, skin, testis, thyroid, pancreas, gut, kidney adrenal and liver) act in an autocrine or paracrine fashion. See Bicknell, *J. Neuroendocrinology* 20: 692-99 (2008).

[0007] POMC peptides, including ACTH, are believed to act primarily through melanocortin receptors (MCRs), a family of five G protein-coupled receptors (i.e., MC1R, MC2R, MC3R, MC4R and MC5R). MCRs are expressed in diverse tissues, and serve discrete physiological functions. MC1R, which is expressed on melanocytes, macrophages and adipocytes, is involved in pigmentation and inflammation. MC2R, which is expressed in the adrenal cortex, is involved in adrenal steroidogenesis. MC3R, which is expressed in the central nervous system (CNS), gastrointestinal (GI) tract and kidney, is involved in energy homeostasis and inflammation. MC4R, which is expressed in the CNS and spinal cord, is involved in energy homeostasis, appetite regulation and erectile function. MC5R, which is expressed on lymphocytes and exocrine cells, is involved in exocrine function and regulation of sebaceous glands. See Ramachandrappa et al., *Frontiers in Endocrinology* 4:19 (2013).

[0008] MC2R is reported to be unique among the MCR family for being highly specific for ACTH. See, Mountjoy KG et al., *Science* 1992; 257:1248–1251; and Schioth HB et al, *Life Sci* 1996; 59: 797–801. However, while MC3R is the only MCR with significant affinity for gamma-MSH, it can also bind alpha-MSH and ACTH with approximately equal affinity. See Gantz I, et al., *J Biol Chem* 1993; 268: 8246–8250. Also, at extremely high plasma concentrations, ACTH can bind to and activate MC1R resulting in hyperpigmentation, e.g., observed in subjects with familial glucocorticoid

deficiency (FGD) (Turan et al., "An atypical case of familial glucocorticoid deficiency without pigmentation caused by coexistent homozygous mutations in MC2R (T152K) and MC1R (R160W)." *J. Clin. Endocrinol. Metab.* 97E771–E774 (2012)).

[0009] ACTH, one of the major end-products of POMC processing, is a hormone that is essential for normal steroidogenesis and the maintenance of normal adrenal weight. ACTH is secreted by the pituitary gland in response to physiological or psychological stress and its principal effects are increased production and release of corticosteroids. In particular, ACTH is secreted from corticotropes in the anterior lobe (or adenohypophysis) of the pituitary gland in response to the release of the hormone corticotropin-releasing hormone (CRH) by the hypothalamus. Once secreted, ACTH then travels to the adrenal cortex, where it binds to and activates MC2R. Activation of MC2R results in the production of cAMP in the adrenal cell. cAMP binds and activates protein kinase (PKA), which activates the conversion of the lipid cholesterol to the steroid hormone cortisol.

[0010] Cortisol is a hormone that affects numerous biological processes in order to restore homeostasis after stress. Exemplary processes regulated by cortisol include regulating glucose homeostasis, increasing blood pressure, gluconeogenesis, promoting metabolism of glycogen, lipids, and proteins, and suppressing the immune system. Under normal physiological conditions, cortisol levels are tightly regulated. However, in some conditions (including diseases and disorders further described herein), cortisol levels are elevated. The overproduction of cortisol has been shown to have many negative effects, such as damaging the hippocampus, a region of the brain that is critical for cognitive functions and regulation of the hypothalamus/pituitary/adrenal axis; increasing fat deposits, blood pressure levels, and blood sugar levels; bone loss; muscle weakness; and suppression of the immune system. Therefore, elevated cortisol levels may play a role in ACTH-driven hypercortisolism (such as Cushing's Disease or Cushing's Syndrome), obesity, diabetes, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), depression, anxiety disorders, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), muscle atrophies, hypertension, cognitive dysfunction, galactorrhea and metabolic syndromes.

[0011] Aldosterone is a hormone released by the adrenal glands that helps regulate blood pressure. In particular, aldosterone increases the reabsorption of sodium and water and the release of potassium in the kidneys. In some disease conditions, aldosterone levels are elevated. For example, primary and secondary hyperaldosteronism occur when the adrenal gland releases too much of the hormone aldosterone. Primary hyperaldosteronism such as Conn's syndrome results from a problem with the adrenal gland itself that causes the release of too much aldosterone, whereas the excess aldosterone in secondary hyperaldosteronism is caused by something outside the adrenal gland that mimics the primary condition, e.g., by causing the adrenal gland to release too much aldosterone. Primary hyperaldosteronism used to be considered a rare condition, but some experts believe that it

may be the cause of high blood pressure in some patients. Most cases of primary hyperaldosteronism are caused by a noncancerous (benign) tumor of the adrenal gland. The condition is most common in people ages 30-50 years. Secondary hyperaldosteronism is frequently due to high blood pressure and it may also be related to disorders such as cirrhosis of the liver, heart failure, and nephrotic syndrome. Therefore, elevated aldosterone levels may play a role in hyperaldosteronism including primary hyperaldosteronism (such as Conn's syndrome), secondary hyperaldosteronism and familial hyperaldosteronism.

SUMMARY

[0012] The invention in general relates to human, humanized or chimerized anti-human adrenocorticotrophic hormone ("ACTH") antibodies or antibody fragments. In one embodiment, the human, humanized or chimerized anti-ACTH antibody or antibody fragment does not substantially interact with (i.e., bind to) a polypeptide consisting of: (i) the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, and/or (ii) the 22 C-terminal amino acid residues of ACTH ($ACTH_{18-39}$).

[0013] The human, humanized or chimerized anti-ACTH antibody or antibody fragment may be selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR, Fab fragments, Fab' fragments, MetMab like antibodies, monovalent antibody fragments, and $F(ab')_2$ fragments. Additionally, the human, humanized or chimerized anti-ACTH antibody or antibody fragment may substantially or entirely lack N-glycosylation and/or O-glycosylation. In one embodiment, the human, humanized or chimerized anti-ACTH antibody or antibody fragment comprises a human constant domain, e.g., an IgG1, IgG2, IgG3, or IgG4 antibody. In another embodiment, the human, humanized or chimerized anti-ACTH antibody or antibody fragment comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation. For example, the Fc region may contain one or more mutations that alters or eliminates N- and/or O-glycosylation. In one embodiment, the human, humanized or chimerized anti-ACTH antibody or antibody fragment comprises the modified IgG1 heavy chain constant domain polypeptide of SEQ ID NO: 886, 887, or 888.

[0014] In one embodiment, the human, humanized or chimerized anti-ACTH antibody or antibody fragment binds to ACTH with a K_D of less than or equal to $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M. Preferably, the human, humanized or chimerized anti-ACTH antibody or antibody fragment binds to ACTH with a K_D of less than or equal to $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M. More preferably, the human, humanized or chimerized anti-ACTH antibody or antibody fragment binds to ACTH with a K_D that is less than about 100 nM, less than about 10 nM, less than about 1 nM, less than about 100 pM, less than about 50 pM, less than about 40

pM, less than about 25 pM, less than about 1 pM, between about 10 pM and about 100 pM, between about 1 pM and about 100 pM, or between about 1 pM and about 10 pM. In exemplary embodiments the K_D value may be detected by surface plasmon resonance (e.g., BIAcore®) at 25° or 37° C. However, other methods such as ELISA and KINEXA may alternatively be used.

[0015] In another embodiment, the human, humanized or chimerized anti-ACTH antibody or antibody fragment binds to ACTH with an off-rate (k_d) of less than or equal to $5x10^{-4}$ s^{-1}, 10^{-4} s^{-1}, $5x10^{-5}$ s^{-1}, or 10^{-5} s^{-1}.

[0016] In yet another embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment that specifically binds to the linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12, preferably Ab2 or Ab3. In particular, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment specifically binds to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12, preferably Ab2 or Ab3. The epitope(s) may be identified using a binding assay that detects the binding of said anti-human ACTH antibody or antibody fragment to one or more peptides in a library of overlapping linear peptide fragments that span the full length of human ACTH. Preferably, the epitope is identified using alanine scanning mutation strategy.

[0017] In yet another embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment that specifically binds to the linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, preferably Ab2.H. In particular, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment specifically binds to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, preferably Ab2.H. The epitope(s) may be identified using a binding assay that detects the binding of said anti-human ACTH antibody or antibody fragment to one or more peptides in a library of overlapping linear peptide fragments that span the full length of human ACTH. Preferably, the epitope is identified using alanine scanning mutation strategy.

[0018] In some embodiments, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment contains at least 2 complementarity determining regions (CDRs), at least 3 CDRs, at least 4 CDRs, at least 5 CDRs or all six CDRs of an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12. In exemplary embodiments, the antibody or fragment will retain the variable heavy chain (V_H) CDR3

and/or the variable light chain (V_L) CDR3 of one of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, or Ab12.

[0019] In some embodiments, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment contains at least 2 complementarity determining regions (CDRs), at least 3 CDRs, at least 4 CDRs, at least 5 CDRs or all six CDRs of an anti-human ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H. In exemplary embodiments, the antibody or fragment will retain the V_H CDR3 and/or the V_L CDR3 of one of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, or Ab12.H.

[0020] In a specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:4; a CDR2 sequence consisting of SEQ ID NO:6; and a CDR3 sequence consisting of SEQ ID NO:8; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:24; a CDR2 sequence consisting of SEQ ID NO:26; and a CDR3 sequence consisting of SEQ ID NO:28. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 2 and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:22. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:2, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:22. More specifically, the anti-human ACTH antibody or antibody fragment may comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO:1, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:21.

[0021] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:44; a CDR2 sequence consisting of SEQ ID NO:46; and a CDR3 sequence consisting of SEQ ID NO:48; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:64; a CDR2 sequence consisting of SEQ ID NO:66; and a CDR3 sequence consisting of SEQ ID NO:68. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:42, and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:62. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:42, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:62. More

specifically, the anti-human ACTH antibody or antibody fragment may comprise (a) a heavy chain having the amino acid sequence of SEQ ID NO:41, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:61.

[0022] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:84; a CDR2 sequence consisting of SEQ ID NO:86; and a CDR3 sequence consisting of SEQ ID NO:88; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:104; a CDR2 sequence consisting of SEQ ID NO:106; and a CDR3 sequence consisting of SEQ ID NO:108. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:82, and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:102. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:82, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:102. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:81, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:101.

[0023] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:124; a CDR2 sequence consisting of SEQ ID NO:126; and a CDR3 sequence consisting of SEQ ID NO:128; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:144; a CDR2 sequence consisting of SEQ ID NO:146; and a CDR3 sequence consisting of SEQ ID NO:148. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:122 and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:142. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:122, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:142. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:121, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:141.

[0024] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:164; a CDR2 sequence consisting of SEQ ID NO:166; and a CDR3

sequence consisting of SEQ ID NO:168; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:184; a CDR2 sequence consisting of SEQ ID NO:186; and a CDR3 sequence consisting of SEQ ID NO:188. Alternatively, the anti-human ACTH antibody or antibody fragment may comprises (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:162, and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:182. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:162, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:182. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:161, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:181.

[0025] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:204; a CDR2 sequence consisting of SEQ ID NO:206; and a CDR3 sequence consisting of SEQ ID NO:208; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:224; a CDR2 sequence consisting of SEQ ID NO:226; and a CDR3 sequence consisting of SEQ ID NO:228. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:202 and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:222. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:202, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:222. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:201, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:221.

[0026] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:244; a CDR2 sequence consisting of SEQ ID NO:246; and a CDR3 sequence consisting of SEQ ID NO:248; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:264; a CDR2 sequence consisting of SEQ ID NO:266; and a CDR3 sequence consisting of SEQ ID NO:268. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:242 and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%,

96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:262. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:242, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:262. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:241, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:261.

[0027] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:284; a CDR2 sequence consisting of SEQ ID NO:286; and a CDR3 sequence consisting of SEQ ID NO:288; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:304; a CDR2 sequence consisting of SEQ ID NO:306; and a CDR3 sequence consisting of SEQ ID NO:308. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:282, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:302. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:282, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:302. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:281, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:301.

[0028] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:324; a CDR2 sequence consisting of SEQ ID NO:326; and a CDR3 sequence consisting of SEQ ID NO:328; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:344; a CDR2 sequence consisting of SEQ ID NO:346; and a CDR3 sequence consisting of SEQ ID NO:348. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:322, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:342. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:322, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:342. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:321, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:341.

[0029] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:364; a CDR2 sequence consisting of SEQ ID NO:366; and a CDR3 sequence consisting of SEQ ID NO:368; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:384; a CDR2 sequence consisting of SEQ ID NO:386; and a CDR3 sequence consisting of SEQ ID NO:388. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:362, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:382. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:362, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:382. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:361, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:381.

[0030] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:404; a CDR2 sequence consisting of SEQ ID NO:406; and a CDR3 sequence consisting of SEQ ID NO:408; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:424; a CDR2 sequence consisting of SEQ ID NO:426; and a CDR3 sequence consisting of SEQ ID NO:428. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:402, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:422. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:402, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:422. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:401, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:421.

[0031] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:444; a CDR2 sequence consisting of SEQ ID NO:446; and a CDR3 sequence consisting of SEQ ID NO:448; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:464; a CDR2 sequence consisting of SEQ ID NO:466; and a CDR3 sequence consisting of SEQ ID NO:468. Alternatively, the anti-human ACTH antibody or

antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:442 and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:462. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:442, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:462. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:441, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:461.

[0032] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:484; a CDR2 sequence consisting of SEQ ID NO:486; and a CDR3 sequence consisting of SEQ ID NO:488; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:504; a CDR2 sequence consisting of SEQ ID NO:506; and a CDR3 sequence consisting of SEQ ID NO:508. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:482, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:502. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:482, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:502. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:481, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:501.

[0033] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:524; a CDR2 sequence consisting of SEQ ID NO:526; and a CDR3 sequence consisting of SEQ ID NO:528; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:544; a CDR2 sequence consisting of SEQ ID NO:546; and a CDR3 sequence consisting of SEQ ID NO:548. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:522, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:542. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:522, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:542. More

specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:521, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:541.

[0034] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:564; a CDR2 sequence consisting of SEQ ID NO:566; and a CDR3 sequence consisting of SEQ ID NO:568; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:584; a CDR2 sequence consisting of SEQ ID NO:586; and a CDR3 sequence consisting of SEQ ID NO:588. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:562, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:582. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:562, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:582. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:561, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:581.

[0035] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:604; a CDR2 sequence consisting of SEQ ID NO:606; and a CDR3 sequence consisting of SEQ ID NO:608; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:624; a CDR2 sequence consisting of SEQ ID NO:626; and a CDR3 sequence consisting of SEQ ID NO:628. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:602, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:622. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:602, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:622. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:601, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:621.

[0036] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:644; a CDR2 sequence consisting of SEQ ID NO:646; and a CDR3

sequence consisting of SEQ ID NO:648; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:664; a CDR2 sequence consisting of SEQ ID NO:666; and a CDR3 sequence consisting of SEQ ID NO:668. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:642 and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:662. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:642, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:662. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:641, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:661.

[0037] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:684; a CDR2 sequence consisting of SEQ ID NO:686; and a CDR3 sequence consisting of SEQ ID NO:688; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:704; a CDR2 sequence consisting of SEQ ID NO:706; and a CDR3 sequence consisting of SEQ ID NO:708. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:682, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:702. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:682, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:702. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:681, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:701.

[0038] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:724; a CDR2 sequence consisting of SEQ ID NO:726; and a CDR3 sequence consisting of SEQ ID NO:728; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:744; a CDR2 sequence consisting of SEQ ID NO:746; and a CDR3 sequence consisting of SEQ ID NO:748. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:722, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%,

97%, 98%, or 99% sequence identity to SEQ ID NO:742. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:722, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:742. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:721, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:741.

[0039] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:764; a CDR2 sequence consisting of SEQ ID NO:766; and a CDR3 sequence consisting of SEQ ID NO:768; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:784; a CDR2 sequence consisting of SEQ ID NO:786; and a CDR3 sequence consisting of SEQ ID NO:788. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:762, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:782. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:762, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:782. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:761, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:781.

[0040] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:804; a CDR2 sequence consisting of SEQ ID NO:806; and a CDR3 sequence consisting of SEQ ID NO:808; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:824; a CDR2 sequence consisting of SEQ ID NO:826; and a CDR3 sequence consisting of SEQ ID NO:828. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:802, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:822. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:802, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:822. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:801, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:821.

[0041] In another specific embodiment, the human, humanized or chimerized anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:844; a CDR2 sequence consisting of SEQ ID NO:846; and a CDR3 sequence consisting of SEQ ID NO:848; and/or (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:864; a CDR2 sequence consisting of SEQ ID NO:866; and a CDR3 sequence consisting of SEQ ID NO:868. Alternatively, the anti-human ACTH antibody or antibody fragment may comprise (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:842 and/or (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:862. Preferably, the anti-human ACTH antibody or antibody fragment comprises (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:842, and/or (b) a variable light chain having the amino acid sequence of SEQ ID NO:862. More specifically, the anti-human ACTH antibody or antibody fragment comprises (a) a heavy chain having the amino acid sequence of SEQ ID NO:841, and/or (b) a light chain having the amino acid sequence of SEQ ID NO:861.

[0042] In one embodiment, the anti-human ACTH antibody or antibody fragments are selected from the group consisting of chimeric, humanized, and human antibodies or antibody fragments, preferably human, humanized or chimerized antibodies or antibody fragments, which may be selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR, Fab fragments, Fab' fragments, MetMab like antibodies, monovalent antibody fragments, and $F(ab')_2$ fragments.

[0043] The anti-human ACTH antibody or antibody fragment may substantially or entirely lack N-glycosylation and/or O-glycosylation. The anti-human ACTH antibody or antibody fragment may comprise a human constant domain, e.g., IgG1, IgG2, IgG3, or IgG4. For example, the heavy chain may comprise the constant domain polypeptide of SEQ ID NO: 886, 887, or 888. In one aspect, the anti-human ACTH antibody or antibody fragment comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation. For example, the Fc region may contain one or more mutations that alters or eliminates N- and/or O-glycosylation.

[0044] In another embodiment, the anti-human ACTH antibody or antibody fragment is directly or indirectly attached to another moiety, such as a detectable label or therapeutic agent.

[0045] In another embodiment, the anti-human ACTH antibody or antibody fragment inhibits or neutralizes at least one biological effect elicited by ACTH when such antibody is administered to a human subject. For example, the antibody or antibody fragment is capable of inhibiting the binding of ACTH to an MCR, i.e., MC1R MC2R, MC3R, MC4R and/or MC5R. Preferably, the anti-human ACTH antibody or antibody fragment neutralizes or inhibits ACTH activation of MC2R; at least one of MC1R, MC2R, MC3R, MC4R and MC5R; at least one of MC2R, MC3R, and MC4R; each of MC2R, MC3R, and MC4R; or each of MC1R, MC2R, MC3R, MC4R and MC5R.

[0046] In one embodiment, the anti-human ACTH antibody or antibody fragment inhibits ACTH-induced cortisol, corticosterone and/or aldosterone secretion. The anti-human ACTH antibody or antibody fragment, when administered to a human subject, may also reduce plasma cortisol, corticosterone, and/or aldosterone levels. In embodiments, the anti-ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels. The anti-ACTH antibody may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[0047] In one embodiment, the anti-human ACTH antibody or antibody fragment binds to ACTH with a K_D that is less than about 100 nM, less than about 10 nM, less than about 1 nM, less than about 100 pM, less than about 50 pM, less than about 40 pM, less than about 25 pM, less than about 1 pM, between about 10 pM and about 100 pM, between about 1 pM and about 100 pM, or between about 1 pM and about 10 pM.

[0048] Preferably, the anti-human ACTH antibody or antibody fragment has stronger affinity for $ACTH_{1-39}$ as compared to alpha-MSH or CLIP, i.e., although there is some cross-reactivity, the antibodies preferentially bind to $ACTH_{1-39}$ as compared to alpha-MSH or CLIP. For example, the affinity of said antibody or antibody fragment to $ACTH_{1-39}$ is at least 10-fold, 100-fold, 1000-fold or stronger than the affinity of said antibody or antibody fragment to alpha-MSH or CLIP (e.g., the K_D of said antibody or fragment for binding to human ACTH is 10-, 100-, or 1000-fold lower than the K_D for binding to alpha-MSH or CLIP).

[0049] More preferably, for example, the anti-human ACTH antibody or antibody fragment binds to $ACTH_{1-39}$ but does not bind to alpha-MSH.

[0050] In one embodiment, the anti-human ACTH antibody or antibody fragment is attached to at least one effector moiety, e.g., which comprises a chemical linker. In another embodiment, the anti-human ACTH antibody or antibody fragment is attached to one or more detectable moieties, e.g., which comprises a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixtures thereof.

[0051] In one embodiment, the anti-human ACTH antibody or antibody fragment is attached to one or more functional moieties.

[0052] The invention also contemplates antibodies, e.g., anti-idiotypic antibodies, produced against an anti-human ACTH antibody or antibody fragment as described above. Furthermore, the invention provides a method of using the anti-idiotypic antibody to monitor the *in vivo* levels of said anti-ACTH antibody or antibody fragment in a subject or to neutralize said anti-ACTH antibody in a subject being administered said anti-ACTH antibody or antibody fragment.

[0053] Moreover, the present invention encompasses a composition suitable for therapeutic, prophylactic, or a diagnostic use comprising a therapeutically, prophylactically or diagnostically effective amount of at least one anti-human ACTH antibody or antibody fragment as described herein. The composition may be suitable for subcutaneous administration, intravenous administration, and/or

topical administration. The composition may be lyophilized. In some embodiments, the composition further comprises a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, or mixture thereof. Additionally, in some embodiments, the composition further comprises another active agent, e.g., selected from the group consisting of ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), and satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil (Provigil®). Additionally, in other embodiments, the composition may be used in conjunction with supplemental oxygen, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), expiratory positive airway pressure (EPAP), adaptive servo-ventilation (ASV), oral appliances, uvulopalatopharyngoplasty (UPPP), maxillomandibular advancement, nasal surgery, and removal of tonsils and/or adenoids to treat sleep apnea.

[0054] In some embodiments, a composition containing the subject antibody may further comprise another active agent, or a therapeutic regimen comprising administration of the subject antibody may include administration of at least one other agent. Said other agent or agents may be an agent that treats a condition associated with ACTH, such as ACTH-driven hypercortisolism, acute coronary syndrome, acute heart failure, Alzheimer's disease, anxiety disorders, atherosclerosis, atrial fibrillation, cachexia, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), cardiac conditions, cardiac fibrosis, cardiovascular disorders, chronic renal failure, chronic stress syndrome, cognitive dysfunction, congestive heart failure, Conn's syndrome, coronary heart diseases, Cushing's Disease, Cushing's Syndrome, depression, diabetes, endothelial dysfunction, exercise intolerance, familial hyperaldosteronism, fibrosis, galactorrhea, heart failure, hyperaldosteronism, hypercortisolemia, hypertension, hyperinsulinemia, hypokalemia, impaired cardiac function, increased formation of collagen, inflammation, metabolic syndrome, muscle atrophy, conditions associated with muscle atrophy, myocardiac fibrosis, nephropathy, obesity, post-myocardial infarction, primary hyperaldosteronism, remodeling following hypertension, renal failure, restenosis, secondary hyperaldosteronism, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), stress related conditions, or syndrome X, or a condition that may co-present with one or more of said conditions, such as hypercholesterolemia. Said additional agent or agents may include without limitation thereto one or more of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists,

Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-1 mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, cholesteryl ester transfer protein (CETP) inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor (milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), or Zestril (lisinopril).

[0055] The present invention further contemplates an isolated nucleic acid sequence or nucleic acid sequences encoding an anti-human ACTH antibody or antibody fragment described herein as well as a vector or vectors containing these isolated nucleic acid sequence or sequences. Additionally, the invention provides a host cell comprising these isolated nucleic acid sequence or sequences or the vector or set forth above. The host cell may be a mammalian, bacterial, fungal, yeast, avian or insect

cell. Preferably, the host cell is a filamentous fungi or a yeast. More preferably, the yeast is selected from the from the following genera: *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*. More preferably, the yeast species is of the genus *Pichia*. Most preferably, the species of *Pichia* is selected from *Pichia pastoris*, *Pichia methanolica* and *Hansenula polymorpha* (*Pichia angusta*).

[0056] The invention further provides a method of expressing an anti-human ACTH antibody or antibody fragment, typically a human, humanized, or chimeric antibody or antibody fragment, the method comprising culturing the host cell described herein under conditions that provide for expression of said antibody or antibody fragment. The host cell may be a polyploid yeast culture that stably expresses and secretes into the culture medium at least 10-25 mg/liter of said antibody or antibody fragment. The polyploid yeast may be made by a method that comprises: (i) introducing at least one expression vector containing one or more heterologous polynucleotides encoding said antibody operably linked to a promoter and a signal sequence into a haploid yeast cell; (ii) producing a polyploid yeast from said first and/or second haploid yeast cell by mating or spheroplast fusion; (iii) selecting a polyploid yeast cell that stably expresses said antibody; and (iv) producing stable polyploid yeast cultures from said polyploid yeast cell that stably expresses said antibody into the culture medium. Preferably, the yeast species is of the genus Pichia.

[0057] The invention further relates to the therapeutic and diagnostic uses of anti-ACTH antibodies and antibody fragments. In one embodiment, the invention provides a method for blocking, inhibiting or neutralizing one or more biological effects associated with ACTH and/or treating any condition associated with elevated cortisol levels comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment. Also, the invention provides a method for treating or preventing a condition associated with elevated ACTH levels in a subject, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment. Exemplary conditions include, but are not limited to, ACTH-driven hypercortisolism (Cushing's Disease and/or Cushing's Syndrome), obesity, diabetes, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), depression, anxiety disorders, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), muscle atrophies, hypertension, cognitive dysfunction, galactorrhea, metabolic syndromes, and hyperaldosteronism including primary hyperaldosteronism (such as Conn's syndrome), secondary hyperaldosteronism, familial hyperaldosteronism, and other conditions associated with ACTH described herein.

[0058] The invention further provides a method for neutralizing ACTH-induced MCR signaling, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment. Moreover, the invention encompasses a method for inhibiting ACTH-induced cortisol, corticosterone, and/or aldosterone secretion, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment. Furthermore, the invention contemplates a method for reducing ACTH-induced plasma cortisol, corticosterone, and/or aldosterone levels in a subject in need thereof, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment. The anti-ACTH antibody may reduce plasma cortisol levels. The anti-ACTH antibody may reduce, but may not abolish, plasma cortisol levels. The anti-ACTH antibody may reduce, but may not abolish, plasma corticosterone levels.

[0059] In these methods, the anti-human ACTH antibody or antibody fragment preferably does not substantially interact with (bind) a polypeptide consisting of: (i) the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, or (ii) the 22 C-terminal amino acid residues of ACTH ($ACTH_{18-39}$).

[0060] In exemplary embodiments in these methods, the anti-human ACTH antibody or antibody fragment, preferably a human, humanized or chimerized anti-ACTH antibody or antibody fragment binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 and preferably the at least one isolated anti-human ACTH antibody or antibody fragment inhibits ACTH-induced signaling via a MCR, e.g., an MCR is selected from the group consisting of MC1R, MC2R, MC3R, MC4R and MC5R.

[0061] In exemplary embodiments in these methods, the anti-human ACTH antibody or antibody fragment, preferably a human, humanized or chimerized anti-ACTH antibody or antibody fragment binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, preferably Ab2.H and preferably the at least one isolated anti-human ACTH antibody or antibody fragment inhibits ACTH-induced signaling via a MCR, e.g., an MCR is selected from the group consisting of MC1R, MC2R, MC3R, MC4R and MC5R.

[0062] In exemplary embodiments the epitope(s) bound by the administered anti-human ACTH antibody or antibody fragment is identified using a binding assay that detects the binding of said anti-human ACTH antibody or antibody fragment to one or more peptides in a library of overlapping linear peptide fragments that span the full length of human ACTH.

[0063] In exemplary embodiments, the methods will use anti-human ACTH antibodies or antibody fragments contain at least 2 complementarity determining regions (CDRs) of an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12. In exemplary embodiments, the antibody or fragment will retain the V_H CDR3 and/or the V_L CDR3 of one of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, or Ab12.

[0064] In exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments contain at least 3 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12.

[0065] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments contain at least 4 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12.

[0066] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments contain at least 5 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12.

[0067] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments contain all 6 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12.

[0068] In exemplary embodiments, the methods will use anti-human ACTH antibodies or antibody fragments contain at least 2 complementarity determining regions (CDRs) of an anti-human ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, preferably Ab2.H. In exemplary embodiments, the antibody or fragment will retain the V_H CDR3 and/or the V_L CDR3 of one of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, or Ab12.H, preferably Ab2.H.

[0069] In exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments contain at least 3 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, preferably Ab2.H.

[0070] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments contain at least 4 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, preferably Ab2.H.

[0071] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments contain at least 5 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, preferably Ab2.H.

[0072] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments contain all 6 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, preferably Ab2.H.

[0073] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:4; a CDR2 sequence consisting of SEQ ID NO:6; and a CDR3 sequence consisting of SEQ ID NO:8; and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:24; a CDR2 sequence consisting of SEQ ID NO:26; and a CDR3 sequence consisting of SEQ ID NO:28; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 2; and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:22; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:2; and/or a variable light chain having the amino acid sequence of SEQ ID NO:22; or (d) a heavy chain having the amino acid sequence of SEQ ID NO:1, and/or a light chain having the amino acid sequence of SEQ ID NO:21.

[0074] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:44; a CDR2 sequence consisting of SEQ ID NO:46; and a CDR3 sequence consisting of SEQ ID NO:48, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:64; a CDR2 sequence consisting of SEQ ID NO:66; and a CDR3 sequence consisting of SEQ ID NO:68; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:42, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:62; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:42, and/or a variable light chain having the amino acid sequence of SEQ ID NO:62; or (d) a heavy chain having the amino acid sequence of SEQ ID NO:41, and/or a light chain having the amino acid sequence of SEQ ID NO:61.

[0075] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:84; a CDR2 sequence consisting of SEQ ID NO:86; and a CDR3 sequence consisting of SEQ ID NO:88, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:104; a CDR2 sequence consisting of SEQ ID NO:106; and a CDR3 sequence consisting of SEQ ID NO:108; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:82, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity

to SEQ ID NO:102; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:82, and/or a variable light chain having the amino acid sequence of SEQ ID NO:102; or (d) a heavy chain having the amino acid sequence of SEQ ID NO:81, and/or a light chain having the amino acid sequence of SEQ ID NO:101.

[0076] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:124; a CDR2 sequence consisting of SEQ ID NO:126 and a CDR3 sequence consisting of SEQ ID NO:128, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:144; a CDR2 sequence consisting of SEQ ID NO:146; and a CDR3 sequence consisting of SEQ ID NO:148; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:122 and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:142; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:122, and/or a variable light chain having the amino acid sequence of SEQ ID NO:142; or (d) a heavy chain having the amino acid sequence of SEQ ID NO:121, and/or a light chain having the amino acid sequence of SEQ ID NO:141.

[0077] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:164; a CDR2 sequence consisting of SEQ ID NO:166; and a CDR3 sequence consisting of SEQ ID NO:168, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:184; a CDR2 sequence consisting of SEQ ID NO:186; and a CDR3 sequence consisting of SEQ ID NO:188; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:162, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:182; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:162, and/or a variable light chain having the amino acid sequence of SEQ ID NO:182; or (d) a heavy chain having the amino acid sequence of SEQ ID NO:161, and/or a light chain having the amino acid sequence of SEQ ID NO:181.

[0078] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:204; a CDR2 sequence consisting of SEQ ID NO:206; and a CDR3 sequence consisting of SEQ ID NO:208, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:224; a CDR2 sequence consisting of SEQ ID NO:226; and a CDR3 sequence consisting of SEQ ID NO:228; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:202 and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99% sequence identity to SEQ ID NO:222; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:202, and/or a variable light chain having the amino acid sequence of SEQ ID NO:222; or (d) a heavy chain having the amino acid sequence of SEQ ID NO:201, and/or a light chain having the amino acid sequence of SEQ ID NO:221.

[0079] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:244; a CDR2 sequence consisting of SEQ ID NO:246; and a CDR3 sequence consisting of SEQ ID NO:248, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:264; a CDR2 sequence consisting of SEQ ID NO:266; and a CDR3 sequence consisting of SEQ ID NO:268; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:242, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:262; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:242, and/or a variable light chain having the amino acid sequence of SEQ ID NO:262; (d) a heavy chain having the amino acid sequence of SEQ ID NO:241, and/or a light chain having the amino acid sequence of SEQ ID NO:261.

[0080] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:284; a CDR2 sequence consisting of SEQ ID NO:286; and a CDR3 sequence consisting of SEQ ID NO:288, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:304; a CDR2 sequence consisting of SEQ ID NO:306; and a CDR3 sequence consisting of SEQ ID NO:308; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:282, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:302; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:282, and/or a variable light chain having the amino acid sequence of SEQ ID NO:302; (d) a heavy chain having the amino acid sequence of SEQ ID NO:281, and/or a light chain having the amino acid sequence of SEQ ID NO:301.

[0081] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:324; a CDR2 sequence consisting of SEQ ID NO:326; and a CDR3 sequence consisting of SEQ ID NO:328, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:344; a CDR2 sequence consisting of SEQ ID NO:346; and a CDR3 sequence consisting of SEQ ID NO:348; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:322, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99% sequence identity to SEQ ID NO:342; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:322, and/or a variable light chain having the amino acid sequence of SEQ ID NO:342; (d) a heavy chain having the amino acid sequence of SEQ ID NO:321, and/or a light chain having the amino acid sequence of SEQ ID NO:341.

[0082] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:364; a CDR2 sequence consisting of SEQ ID NO:366; and a CDR3 sequence consisting of SEQ ID NO:368, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:384; a CDR2 sequence consisting of SEQ ID NO:386; and a CDR3 sequence consisting of SEQ ID NO:388; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:362, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:382; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:362, and/or a variable light chain having the amino acid sequence of SEQ ID NO:382; (d) a heavy chain having the amino acid sequence of SEQ ID NO:361, and/or a light chain having the amino acid sequence of SEQ ID NO:381.

[0083] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:404; a CDR2 sequence consisting of SEQ ID NO:406; and a CDR3 sequence consisting of SEQ ID NO:408, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:424; a CDR2 sequence consisting of SEQ ID NO:426; and a CDR3 sequence consisting of SEQ ID NO:428; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:402, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:422; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:402, and/or a variable light chain having the amino acid sequence of SEQ ID NO:422; (d) a heavy chain having the amino acid sequence of SEQ ID NO:401, and/or a light chain having the amino acid sequence of SEQ ID NO:421.

[0084] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:444; a CDR2 sequence consisting of SEQ ID NO:446; and a CDR3 sequence consisting of SEQ ID NO:448, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:464; a CDR2 sequence consisting of SEQ ID NO:466; and a CDR3 sequence consisting of SEQ ID NO:468; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:442, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99% sequence identity to SEQ ID NO:462; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:442, and/or a variable light chain having the amino acid sequence of SEQ ID NO:462; (d) a heavy chain having the amino acid sequence of SEQ ID NO:441, and/or a light chain having the amino acid sequence of SEQ ID NO:461.

[0085] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:484; a CDR2 sequence consisting of SEQ ID NO:486; and a CDR3 sequence consisting of SEQ ID NO:488, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:504; a CDR2 sequence consisting of SEQ ID NO:506; and a CDR3 sequence consisting of SEQ ID NO:508; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:482, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:502; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:482, and/or a variable light chain having the amino acid sequence of SEQ ID NO:502; (d) a heavy chain having the amino acid sequence of SEQ ID NO:481, and/or a light chain having the amino acid sequence of SEQ ID NO:501.

[0086] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:524; a CDR2 sequence consisting of SEQ ID NO:526; and a CDR3 sequence consisting of SEQ ID NO:528, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:544; a CDR2 sequence consisting of SEQ ID NO:546; and a CDR3 sequence consisting of SEQ ID NO:548; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:522, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:542; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:522, and/or a variable light chain having the amino acid sequence of SEQ ID NO:542; (d) a heavy chain having the amino acid sequence of SEQ ID NO:521, and/or a light chain having the amino acid sequence of SEQ ID NO:541.

[0087] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:564; a CDR2 sequence consisting of SEQ ID NO:566; and a CDR3 sequence consisting of SEQ ID NO:568, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:584; a CDR2 sequence consisting of SEQ ID NO:586; and a CDR3 sequence consisting of SEQ ID NO:588; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:562, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99% sequence identity to SEQ ID NO:582; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:562, and/or a variable light chain having the amino acid sequence of SEQ ID NO:582; (d) a heavy chain having the amino acid sequence of SEQ ID NO:561, and/or a light chain having the amino acid sequence of SEQ ID NO:581.

[0088] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:604; a CDR2 sequence consisting of SEQ ID NO:606; and a CDR3 sequence consisting of SEQ ID NO:608, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:624; a CDR2 sequence consisting of SEQ ID NO:626; and a CDR3 sequence consisting of SEQ ID NO:628; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:602, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:622; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:602, and/or a variable light chain having the amino acid sequence of SEQ ID NO:622; (d) a heavy chain having the amino acid sequence of SEQ ID NO:601, and/or a light chain having the amino acid sequence of SEQ ID NO:621.

[0089] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:644; a CDR2 sequence consisting of SEQ ID NO:646; and a CDR3 sequence consisting of SEQ ID NO:648, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:664; a CDR2 sequence consisting of SEQ ID NO:666; and a CDR3 sequence consisting of SEQ ID NO:668; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:642, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:662; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:642, and/or a variable light chain having the amino acid sequence of SEQ ID NO:662; (d) a heavy chain having the amino acid sequence of SEQ ID NO:641, and/or a light chain having the amino acid sequence of SEQ ID NO:661.

[0090] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:684; a CDR2 sequence consisting of SEQ ID NO:686; and a CDR3 sequence consisting of SEQ ID NO:688, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:704; a CDR2 sequence consisting of SEQ ID NO:706; and a CDR3 sequence consisting of SEQ ID NO:708; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:682, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99% sequence identity to SEQ ID NO:702; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:682, and/or a variable light chain having the amino acid sequence of SEQ ID NO:702; (d) a heavy chain having the amino acid sequence of SEQ ID NO:681, and/or a light chain having the amino acid sequence of SEQ ID NO:701.

[0091] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:724; a CDR2 sequence consisting of SEQ ID NO:726; and a CDR3 sequence consisting of SEQ ID NO:728, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:744; a CDR2 sequence consisting of SEQ ID NO:746; and a CDR3 sequence consisting of SEQ ID NO:748; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:722, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:742; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:722, and/or a variable light chain having the amino acid sequence of SEQ ID NO:742; (d) a heavy chain having the amino acid sequence of SEQ ID NO:721, and/or a light chain having the amino acid sequence of SEQ ID NO:741.

[0092] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:764; a CDR2 sequence consisting of SEQ ID NO:766; and a CDR3 sequence consisting of SEQ ID NO:768, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:784; a CDR2 sequence consisting of SEQ ID NO:786; and a CDR3 sequence consisting of SEQ ID NO:788; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:762, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:782; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:762, and/or a variable light chain having the amino acid sequence of SEQ ID NO:782; (d) a heavy chain having the amino acid sequence of SEQ ID NO:761, and/or a light chain having the amino acid sequence of SEQ ID NO:781.

[0093] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:804; a CDR2 sequence consisting of SEQ ID NO:806; and a CDR3 sequence consisting of SEQ ID NO:808, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:824; a CDR2 sequence consisting of SEQ ID NO:826; and a CDR3 sequence consisting of SEQ ID NO:828; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:802, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99% sequence identity to SEQ ID NO:822; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:802, and/or a variable light chain having the amino acid sequence of SEQ ID NO:822; (d) a heavy chain having the amino acid sequence of SEQ ID NO:801, and/or a light chain having the amino acid sequence of SEQ ID NO:821.

[0094] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:844; a CDR2 sequence consisting of SEQ ID NO:846; and a CDR3 sequence consisting of SEQ ID NO:848, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:864; a CDR2 sequence consisting of SEQ ID NO:866; and a CDR3 sequence consisting of SEQ ID NO:868; (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:842, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:862; (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:842, and/or a variable light chain having the amino acid sequence of SEQ ID NO:862; (d) a heavy chain having the amino acid sequence of SEQ ID NO:841, and/or a light chain having the amino acid sequence of SEQ ID NO:861.

[0095] In other exemplary embodiments, the anti-ACTH antibodies or antibody fragments used in the methods are chimeric, humanized, and human antibodies or antibody fragments.

[0096] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR, Fab fragments, Fab' fragments, MetMab like antibodies, monovalent antibody fragments, and $F(ab')_2$ fragments.

[0097] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that substantially or entirely lack N-glycosylation and/or O-glycosylation.

[0098] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise a human constant domain, e.g., an IgG1, IgG2, IgG3, or IgG4 antibody, such as the heavy chain constant domain polypeptide of SEQ ID NO: 886, 887, or 888.

[0099] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that comprise an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation.

[0100] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments having an Fc region which contains one or more mutations that alters or eliminates N- and/or O-glycosylation.

[0101] In other exemplary embodiments, the methods will use a human or humanized anti-ACTH antibody or antibody fragment.

[0102] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that bind to ACTH with a K_D of less than or equal to $5x10^{-5}$ M, 10-5 M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M.

[0103] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that bind to ACTH with a K_D of less than or equal to $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M.

[0104] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that bind to ACTH with an off-rate (k_d) of less than or equal to $5x10^{-4}$ s^{-1}, 10^{-4} s^{-1}, $5x10^{-5}$ s^{-1}, or 10^{-5} s^{-1}.

[0105] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that are directly or indirectly attached to a therapeutic agent.

[0106] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that are attached to one or more detectable moieties.

[0107] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments comprising a detectable moiety, e.g., that comprises a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixtures thereof.

[0108] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that are attached to one or more functional moieties.

[0109] In other exemplary embodiments, the methods will use anti-ACTH antibodies or antibody fragments that reduce plasma cortisol, corticosterone, and/or aldosterone levels. The anti-ACTH antibody may reduce plasma cortisol levels.

[0110] In other exemplary embodiments, the methods further comprise administering separately or co-administering another agent, e.g., selected from the group consisting of ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), and satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil (Provigil®). Further, said additional agent may include without limitation thereto one or more of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-1 mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-

adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor (milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), or Zestril (lisinopril). The antibody or antibody fragment or the composition containing the antibody of antibody fragment and the at least one other agent may be administered concurrently sequentially, e.g., the antibody or antibody fragment is administered before or after the at least one other agent.

[0111] In yet other exemplary embodiments, the methods further comprise using the anti-ACTH antibodies or antibody fragments disclosed herein in combination with supplemental oxygen, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), expiratory positive airway pressure (EPAP), adaptive servo-ventilation (ASV), oral applicanes,

uvulopalatopharyngoplasty (UPPP), maxillomandibular advancement, nasal surgery, and removal of tonsils and/or adenoids to treat sleep apnea.

[0112] In other exemplary methods, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-ACTH antibody or antibody fragment which substantially does not interact with (bind) a polypeptide consisting of: (i) the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, or (ii) the 22 C-terminal amino acid residues of ACTH ($ACTH_{18-39}$) (Corticotrophin-Like Intermediate peptide or "CLIP").

[0113] In other exemplary embodiments, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-ACTH antibody or antibody fragment which binds to $ACTH_{1-39}$ with a binding affinity (K_D) at least 10-fold, 100-fold, 1000-fold or 10,000-fold stronger than the binding affinity of said antibody or antibody fragment to (i) $ACTH_{1-13}$ and/or alpha-MSH, and/or (ii) CLIP (i.e., a numerically lower K_D for $ACTH_{1-39}$ by at least 10-fold, 100-fold, 1000-fold or 10,000-fold relative to the K_D for $ACTH_{1-13}$ and/or alpha-MSH and/or CLIP).

[0114] In other exemplary embodiments, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment which neutralizes or inhibits ACTH activation of MC2R.

[0115] In other exemplary embodiments, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment which neutralizes or inhibits ACTH activation of at least one of MC2R, MC3R and MC4R.

[0116] In other exemplary embodiments, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment, which neutralizes or inhibits ACTH activation of each of MC2R, MC3R and MC4R.

[0117] In other exemplary embodiments, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment, which inhibits ACTH-induced corticosterone secretion. The anti-ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels. The anti-ACTH antibody may reduce plasma corticosterone levels, but may not abolish plasma corticosterone levels.

[0118] In other exemplary embodiments, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment, which when administered to a human subject reduces plasma cortisol, corticosterone and/or aldosterone levels. The anti-ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels. The anti-ACTH antibody may reduce plasma corticosterone levels, but may not abolish plasma corticosterone levels.

[0119] In other exemplary embodiments, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment capable of inhibiting the binding of ACTH to a MCR.

[0120] In other exemplary embodiments, the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment, capable of inhibiting the binding of ACTH to at least one of MC1R, MC2R, MC3R, MC4R and MC5R; at least one of MC2R, MC3R, and MC4R; each of MC2R, MC3R, and MC4R; or each of MC1R, MC2R, MC3R, MC4R and MC5R.

BRIEF DESCRIPTION OF THE DRAWINGS

[0121] FIG. 1A-1G provides the polypeptide sequences of the full-length heavy chain for antibodies Ab1-Ab7 and Ab9-Ab12 (SEQ ID NOs: 1; 41; 81; 121; 161; 201; 241; 281; 321; 361; and 401, respectively) and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H (SEQ ID NOs: 441; 481; 521; 561; 601; 641; 681; 721; 761; 801; and 841; respectively) aligned by their framework regions (FR) and complementarity determining regions (CDRs), and constant regions.

[0122] FIG. 2A-2D provide the polypeptide sequences of the full-length light chain for antibodies Ab1-Ab7 and Ab9-Ab12 (SEQ ID NOs: 21; 61; 101; 141; 181; 221; 261; 301; 341; 381; and 421, respectively) and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H (SEQ ID NOs: 461; 501; 541; 581; 621; 661; 701; 741; 781; 821 and 861, respectively) aligned by their framework regions (FR), complementarity determining regions (CDRs), and constant regions.

[0123] FIG. 3A-3S provide the polynucleotide sequences encoding the full-length heavy chain for antibodies Ab1-Ab7 and Ab9-Ab12 (SEQ ID NOs: 11; 51; 91; 131; 171; 211; 251; 291; 331; 371; and 411, respectively) and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H (SEQ ID NOs: 451; 491; 531; 571; 611; 651; 691; 731; 771; 811; and 851, respectively) aligned by their framework regions (FR), complementarity determining regions (CDRs), and constant regions.

[0124] FIG. 4A-I provide the polynucleotide sequences encoding the full-length light chain for antibodies Ab1-Ab7 and Ab9-Ab12 (SEQ ID NOs: 31; 71; 111; 151; 191; 231; 271; 311; 351; 391; and 431, respectively) and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H (SEQ ID NOs: 471; 511; 551; 591; 631; 671; 711; 751; 791; 831; and 871, respectively) aligned by their framework regions (FR), complementarity determining regions (CDRs), and constant regions.

[0125] FIG. 5 provides the polypeptide sequence coordinates for certain antibody heavy chain protein sequence features including the variable region and complementarity determining regions (CDRs) of the heavy chain for antibodies Ab1-Ab7 and Ab9-Ab12 and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0126] FIG. 6 provides the polypeptide sequence coordinates for certain antibody heavy chain protein sequence features including the constant region and framework regions (FR) of the heavy chain for antibodies Ab1-Ab7 and Ab9-Ab12 and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0127] FIG. 7 provides the polypeptide sequence coordinates for certain antibody light chain protein sequence features including the variable region and complementarity determining regions (CDRs) of the light chain for antibodies Ab1-Ab7 and Ab9-Ab12 and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0128] FIG. 8 provides the polypeptide sequence coordinates for certain antibody light chain protein sequence features including the constant region and framework regions (FR) of the light chain for antibodies Ab1-Ab7 and Ab9-Ab12 and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0129] FIG. 9 provides the polynucleotide sequence coordinates for certain antibody heavy chain DNA sequence features including the variable region and complementarity determining regions (CDRs) of the heavy chain for antibodies Ab1-Ab7 and Ab9-Ab12 and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0130] FIG. 10 provides the polynucleotide sequence coordinates for certain antibody heavy chain DNA sequence features including the constant region and framework regions (FR) of the heavy chain for antibodies Ab1-Ab7 and Ab9-Ab12 and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0131] FIG. 11 provides the polynucleotide sequence coordinates for certain antibody light chain DNA sequence features including the variable region and complementarity determining regions (CDRs) of the light chain for antibodies Ab1-Ab7 and Ab9-Ab12 and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0132] FIG. 12 provides the polynucleotide sequence coordinates for certain antibody light chain DNA sequence features including the constant region and framework regions (FR) of the light chain for antibodies Ab1-Ab7 and Ab9-Ab12 and Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0133] FIG. 13 provides representative binding data for the subject anti-human ACTH antibodies to human ACTH (specifically, for Ab1).

[0134] FIG. 14 provides representative binding data for the subject anti-human ACTH antibodies to human ACTH1-13 and ACTH 18-39 (specifically, for Ab1).

[0135] FIG. 15 provides representative binding data for the subject anti-human ACTH antibodies to ACTH 1-39 and the inability of human ACTH 1-13 and ACTH 18-39 to compete with binding of ACTH 1-39 (specifically, for Ab5).

[0136] FIG. 16 provides representative data showing that the subject anti-ACTH antibodies (in this figure, Ab1) inhibited ACTH-induced cAMP production in cells expressing MC2R.

[0137] FIG. 17 provides representative data showing that the subject anti-ACTH antibodies (in this figure, Ab5) inhibited ACTH-induced cAMP production in cells expressing MC2R.

[0138] FIG. 18 provides representative data showing that the subject anti-ACTH antibodies (in this figure, Ab1) inhibited ACTH-induced cAMP production in cells expressing MC1R.

[0139] FIG. 19 provides representative data showing that the subject anti-ACTH antibodies (in this figure, Ab1) inhibited ACTH-induced cAMP production in cells expressing MC3R.

[0140] FIG. 20 provides representative data showing that the subject anti-ACTH antibodies (in this figure, Ab1) inhibited ACTH-induced cAMP production in cells expressing MC4R.

[0141] FIG. 21 provides representative data showing that the subject anti-ACTH antibodies (in this figure, Ab1) inhibited ACTH-induced cAMP production in cells expressing MC5R.

[0142] FIG. 22 provides representative data showing that the subject anti-ACTH antibodies (in this figure, Ab1) inhibited ACTH-induced cortisol production by Y1 cells.

[0143] FIG. 23 shows plasma corticosterone levels pre-dose of Ab2 or Ab3 for the experiments described in Example 6.

[0144] FIG. 24 shows plasma corticosterone levels 48 hours after the first dose of Ab2, Ab3, or vehicle control (AD26-10) antibody for the experiments described in Example 6.

[0145] FIG. 25 shows plasma corticosterone levels 48 hours after the second dose of Ab2, Ab3, or vehicle control (AD26-10) antibody for the experiments described in Example 6.

[0146] FIG. 26 shows plasma corticosterone levels 120 hours after the second dose of Ab2, Ab3, or vehicle control (AD26-10) antibody for the experiments described in Example 6.

[0147] FIG. 27 shows the percent change in animal weight for animals treated with Ab6 and dosed with ACTH using an infusion pump for the experiments described in Example 7. ANOVA analysis was performed at day 8 to compare Vehicle/control antibody (AD26-10) to ACTH/control antibody (AD26-10) which showed a significant difference ($p < 0.0001$), and to compare ACTH/Ab6 to ACTH/AD26-10 which also showed a significant difference ($p < 0.0001$).

[0148] FIG. 28 shows plasma corticosterone levels before initiation of ACTH dosing and antibody administration for the experiments described in Example 7.

[0149] FIG. 29 shows plasma corticosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose for the experiments described in Example 7.

[0150] FIG. 30 shows plasma corticosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose (Ab6) for the experiments described in Example 7.

[0151] FIG. 31 shows plasma corticosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose (Ab6) for the experiments described in Example 7.

[0152] FIG. 32 shows plasma corticosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose (Ab6) for the experiments described in Example 7.

[0153] FIG. 33 shows plasma corticosterone levels 168 hours post initiation of ACTH dosing and 144 hours post Ab dose (Ab6) for the experiments described in Example 7.

[0154] FIG. 34 shows plasma aldosterone levels before the initiation of ACTH dosing and antibody administration for the experiments described in Example 7.

[0155] FIG. 35 shows plasma aldosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose for the experiments described in Example 7.

[0156] FIG. 36 shows plasma aldosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose (Ab6) for the experiments described in Example 7.

[0157] FIG. 37 shows plasma aldosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose (Ab6) for the experiments described in Example 7.

[0158] FIG. 38 shows plasma aldosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose (Ab6) for the experiments described in Example 7.

[0159] FIG. 39 shows plasma aldosterone levels 168 hours post initiation of ACTH dosing and 144 hours post Ab dose (Ab6) for the experiments described in Example 7.

[0160] FIG. 40A-L shows results of binding kinetics measurements for binding of anti-ACTH antibodies to alanine scanning mutants of human ACTH. Each upper panel shows results for wild-type huACTH and alanine scanning mutants that were determined to substantially affect binding, indicating that these positions formed part of the epitope bound by this antibody. Each lower panel shows traces for all of the remaining alanine scanning mutants (along with wild-type huACTH shown for reference).

[0161] FIG. 41 shows the results of alanine scanning mutagenesis used to identify positions in ACTH that form the epitope bound by each tested antibody. In the column under each antibody name are listed the mutation of which substantially altered the binding kinetics of the antibody to ACTH, which was interpreted to indicate that the position forms part of the epitope bound by that antibody. For visual illustration the positions are listed in order of their position, e.g., the seventh row below the header is labeled "7A" for those antibodies for which the 7A mutant resulted in substantially decreased binding to ACTH. An empty cell indicates a mutant position that did not substantially alter binding kinetics for that antibody. The rows corresponding to positions 24 and beyond are not shown because none of these positions was observed to substantially alter antibody binding kinetics.

[0162] FIG. 42 shows the results of ^{125}I ACTH binding experiments demonstrating that the tested anti-ACTH antibodies inhibited the binding of ACTH to MC2R expressing cells, as further described in Example 9. Each antibody tested is labeled on the X-axis and the level of binding detected is shown on the Y-axis.

[0163] FIG. 43 is a representative binding curve that shows neutralization of ACTH 1-24 induced signaling via MC2R (in this case, by Ab2).

[0164] FIG. 44 shows that Ab1.H inhibited ACTH-induced weight loss in the study described in Example 13.

[0165] FIG. 45 shows plasma corticosterone levels before ACTH and antibody dosing in the study described in Example 13.

[0166] FIG. 46 shows plasma corticosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration in the study described in Example 13.

[0167] FIG. 47 shows plasma corticosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration in the study described in Example 13.

[0168] FIG. 48 shows plasma corticosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration in the study described in Example 13.

[0169] FIG. 49 shows plasma corticosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration in the study described in Example 13.

[0170] FIG. 50 shows plasma corticosterone levels 168 hours after initiation of ACTH dosing and 144 hours after the antibody administration in the study described in Example 13.

[0171] FIG. 51 shows plasma aldosterone levels before ACTH and antibody dosing in the study described in Example 13.

[0172] FIG. 52 shows plasma aldosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration in the study described in Example 13.

[0173] FIG. 53 shows plasma aldosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration in the study described in Example 13.

[0174] FIG. 54 shows plasma aldosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration in the study described in Example 13.

[0175] FIG. 55 shows plasma aldosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration in the study described in Example 13.

[0176] FIG. 56 shows plasma aldosterone levels 168 hours after initiation of ACTH dosing and 144 hours after the antibody administration in the study described in Example 13.

[0177] FIG. 57 shows the percentage change in animal weight by day, and shows that Ab2.H, Ab11.H, and Ab12.H inhibited ACTH-induced weight loss for the study described in Example 14.

[0178] FIG. 58 shows plasma corticosterone levels before ACTH and antibody dosing for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0179] FIG. 59 shows plasma corticosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0180] FIG. 60 shows plasma corticosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0181] FIG. 61 shows plasma corticosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0182] FIG. 62 shows plasma corticosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0183] FIG. 63 shows plasma aldosterone levels before ACTH and antibody dosing for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0184] FIG. 64 shows plasma aldosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0185] FIG. 65 shows plasma aldosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0186] FIG. 66 shows plasma aldosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0187] FIG. 67 shows plasma aldosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration for animals treated with Ab2.H, Ab11.H, and Ab12.H as described in Example 14.

[0188] FIG. 68 shows the percentage change in animal weight by day, and shows that Ab10.H inhibited ACTH-induced weight loss in the study described in Example 14.

[0189] FIG. 69 shows plasma corticosterone levels before ACTH and antibody dosing for animals treated with Ab10.H as described in Example 14.

[0190] FIG. 70 shows plasma corticosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration for animals treated with Ab10.H as described in Example 14.

[0191] FIG. 71 shows plasma corticosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration for animals treated with Ab10.H as described in Example 14.

[0192] FIG. 72 shows plasma corticosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration for animals treated with Ab10.H as described in Example 14.

[0193] FIG. 73 shows plasma corticosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration for animals treated with Ab10.H as described in Example 14.

[0194] FIG. 74 shows plasma aldosterone levels before ACTH and antibody dosing for animals treated with Ab10.H as described in Example 14.

[0195] FIG. 75 shows plasma aldosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration for animals treated with Ab10.H as described in Example 14.

[0196] FIG. 76 shows plasma aldosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration for animals treated with Ab10.H as described in Example 14.

[0197] FIG. 77 shows plasma aldosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration for animals treated with Ab10.H as described in Example 14.

[0198] FIG. 78 shows plasma aldosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration for animals treated with Ab10.H as described in Example 14.

[0199] FIG. 79 shows the percentage change in animal weight by day, and shows that Ab7A.H inhibited ACTH-induced weight loss for the study described in Example 14.

[0200] FIG. 80 shows plasma corticosterone levels before ACTH and antibody dosing for animals treated with Ab7A.H as described in Example 14.

[0201] FIG. 81 shows plasma corticosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration for animals treated with Ab7A.H as described in Example 14.

[0202] FIG. 82 shows plasma corticosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration for animals treated with Ab7A.H as described in Example 14.

[0203] FIG. 83 shows plasma corticosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration for animals treated with Ab7A.H as described in Example 14.

[0204] FIG. 84 shows plasma corticosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration for animals treated with Ab7A.H as described in Example 14.

[0205] FIG. 85 shows plasma aldosterone levels before ACTH and antibody dosing for animals treated with Ab7A.H as described in Example 14.

[0206] FIG. 86 shows plasma aldosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration for animals treated with Ab7A.H as described in Example 14.

[0207] FIG. 87 shows plasma aldosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration for animals treated with Ab7A.H as described in Example 14.

[0208] FIG. 88 shows plasma aldosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration for animals treated with Ab7A.H as described in Example 14.

[0209] FIG. 89 shows plasma aldosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration for animals treated with Ab7A.H as described in Example 14.

[0210] FIG. 90 shows plasma corticosterone levels before ACTH and antibody dosing for animals treated with Ab11A.H as described in Example 14.

[0211] FIG. 91 shows plasma corticosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration for animals treated with Ab11A.H as described in Example 14.

[0212] FIG. 92 shows plasma corticosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration for animals treated with Ab11A.H as described in Example 14.

[0213] FIG. 93 shows plasma corticosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration for animals treated with Ab11A.H as described in Example 14.

DETAILED DESCRIPTION

[0214] Antibodies and binding fragments thereof that bind to ACTH are disclosed herein. The antibody or antibody fragment according to the invention bind to ACTH and prevent ACTH from functioning in various ways. In some embodiments, the antibody or antibody fragment neutralizes ACTH-induced MCR signaling, inhibits ACTH-induced cortisol, corticosterone, and/or aldosterone secretion and/or reduces plasma cortisol, corticosterone, and/or aldosterone levels.

[0215] For convenience, the following sections generally outline the various meanings of the terms used herein. Following this discussion, general aspects regarding antibodies or antibody fragments according to the invention are discussed, followed by specific examples demonstrating the properties of various embodiments of the antibodies or antibody fragments according to the invention and how they can be employed.

[0216] ***Definitions***

[0217] It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the protein" includes reference to one or more

proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

[0218] The terms "adrenocorticotropin" or "adrenocorticotrophin" or "ACTH" or "ACTH 1-39" or "$ACTH_{1-39}$" or "corticotropin" or "corticotrophin" are used interchangeably and refer to the polypeptide as set forth in SEQ ID NO:881 as well as related polypeptides, which include, but are not limited to, derivative variants, substitution variants, deletion variants, and/or insertion variants including the addition of an N-terminal methionine, fusion polypeptides, and interspecies homologs. The terms "human adrenocorticotropin" or "human adrenocorticotrophin" or "hACTH" or "hACTH 1-39" or "$hACTH_{1-39}$" or "huACTH" or "huACTH 1-39" or "$huACTH_{1-39}$" are used interchangeably and refer specifically to a human ACTH polypeptide such as the polypeptide as set forth in SEQ ID NO:881. In certain embodiments, an ACTH polypeptide includes terminal residues, such as, but not limited to, leader sequence residues, targeting residues, amino terminal methionine residues, lysine residues, tag residues, and/or fusion protein residues. ACTH has also been referred to as corticotrophin or corticotropin. ACTH is a peptide hormone produced by post-translational enzymatic processing of POMC. In some tissues, e.g., the intermediate lobe, ACTH is further enzymatically processed to generate alpha-MSH and CLIP. Alpha-MSH has the same primary amino acid sequence as $ACTH_{1-13}$; however, two of the amino acids are modified in alpha-MSH, i.e., the N-terminal serine is acetylated and the C-terminal valine is amidated, but not $ACTH_{1-13}$. CLIP corresponds to $ACTH_{18-39}$.

[0219] Except where the context indicates otherwise, the term "ACTH" as used herein denotes the full-length human ACTH peptide containing 39 amino acids (SYSMEHFRWGKPVGKKRRPVKVYPNGAEDESAEAFPLEF, SEQ ID NO:881). ACTH is distinct from "ACTH 1-13" (SYSMEHFRWGKPV, SEQ ID NO:883), "ACTH 18-39" (RPVKVYPNGAEDESAEAFPLEF, SEQ ID NO:884) and "ACTH 1-24" (SYSMEHFRWGKPVGKKRRPVKVYP, SEQ ID NO:882). However, the term also refers to the ACTH of another species when indicated by context, e.g., equine ACTH or horse ACTH (Equus przewalskii, NCBI Accession No. XP_008513480), feline ACTH or cat ACTH (Felis catus, NCBI Accession No. XP_003984482), and canine ACTH or dog ACTH (canus lupus familiaris, NCBI accession no. AAK08973). The term ACTH also encompasses ACTH molecules incorporating post-translational modifications, e.g., phosphorylation, glycosylation, ubiquitination, acetylation, methylation and/or amidation.

[0220] The term "human alpha-MSH" refers to a peptide that consists of amino acids 1-13 of human ACTH. As discussed herein, alpha-MSH has the same primary amino acid sequence as amino acids 1-13 of human ACTH (also referred to as "ACTH 1-13" or "$ACTH_{1-13}$"), but two of the amino acids are modified in alpha-MSH, specifically, the N-terminal serine is acetylated and the C-terminal

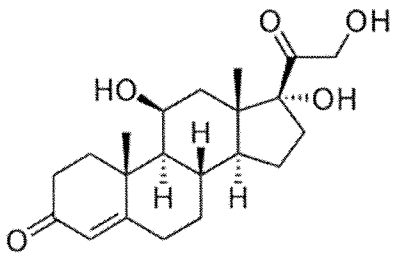
valine is amidated (having the sequence SYSMEHFRWGKPV where S1 is acetylated and V13 is amidated, SEQ ID NO:885). Except where context dictates otherwise, the terms "alpha-MSH" herein indicate human alpha-MSH.

[0221] The terms "human CLIP" or "human Corticotrophin-Like Intermediate Peptide" or "$hACTH_{18-39}$" or "hCLIP" or "ACTH 18-39" are used interchangeably and each refers to a peptide that consists of the 22 C-terminal amino acid residues of human ACTH, i.e., amino acids 18-39 of the human ACTH polypeptide of SEQ ID NO:881 (having the sequence RPVKVYPNGAEDESAEAFPLEF, SEQ ID NO:884). Except where context dictates otherwise, the terms "CLIP" or "Corticotrophin-Like Intermediate Peptide" herein indicate human CLIP.

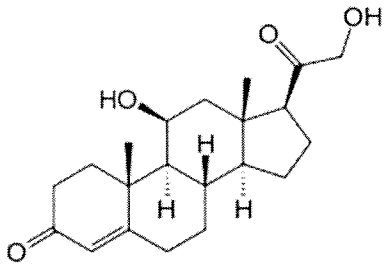
[0222] The term "anti-ACTH antibody or antibody fragment that does not substantially interact with or bind to at least one of $ACTH_{1-13}$, alpha-MSH, and/or $ACTH_{18-39}$ (CLIP)" means that the anti-ACTH antibody or antibody fragment binds to ACTH, typically human ACTH, with a binding affinity (K_D) that is substantially stronger than the binding affinity for said anti-ACTH antibody or antibody fragment to at least one of $ACTH_{1-13}$, alpha-MSH, and/or $ACTH_{18-39}$ (CLIP), i.e., at least 10-fold, 100-fold, 1000-fold or 10,000-fold stronger binding. Binding affinity may be expressed as "K_D" in molar units (e.g., nM or pM), with numerically lower values indicating stronger binding. Thus, a "stronger" affinity refers to a numerically lower K_D value, while a "weaker" affinity refers to a numerically higher K_D value. In exemplary embodiments, said the binding affinity of said antibody for human ACTH will be at least 100-fold stronger than its binding affinity for human CLIP and human alpha-MSH.

[0223] In some instances, this includes anti-ACTH antibodies or antibody fragments thereof that do not detectably bind to $ACTH_{1-13}$, alpha-MSH, and/or $ACTH_{18-39}$ (CLIP) (e.g., several antibodies are designated as having a K_D of 1×10^{-1} for CLIP in Table 5 or are designated as having a K_D of 1×10^{-1} for alpha-MSH in Table 6, which indicates no detectable binding).

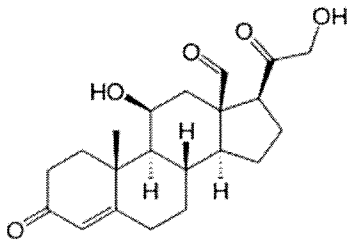
[0224] The term "cortisol" refers to a steroid hormone, more specifically a glucocorticoid, which is produced by the zona fasciculata of the adrenal cortex released in response to stress and a low level of blood glucose. Administration of an anti-ACTH antibody as described herein may reduce plasma cortisol levels. References to a treatment that may "reduce" plasma cortisol levels may refer to decreasing the plasma cortisol level to less than 50%, 40%, 30%, 25%, 20%, 15%, 10%, 5%, 2%, 1%, 0.1%, or 0.01% of the plasma cortisol level prior to treatment (such as anti-ACTH administration). However, plasma cortisol levels may not be abolished. References to a treatment that may "not abolish" plasma cortisol levels may refer to retaining at least 0.01%, 0.1%, 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50% or more of the plasma cortisol level prior to treatment (such as anti-ACTH administration). The systematic (IUPAC) name of cortisol is (11β)-11,17,21-trihydroxypregn-4-ene-3,20-dione and its structure is well known in the art and is shown below:



[0225] The term "Corticosterone" refers to a 21-carbon steroid hormone of the corticosteroid type produced in the cortex of the adrenal glands in rodents and other non-human animals. Administration of an anti-ACTH antibody as described herein may reduce plasma corticosterone levels. References to a treatment that may "reduce" plasma corticosterone levels may refer to decreasing the plasma corticosterone level to less than 50%, 40%, 30%, 25%, 20%, 15%, 10%, 5%, 2%, 1%, 0.1%, or 0.01% of the plasma cortisol level prior to treatment (such as anti-ACTH administration). However, plasma corticosterone levels may not be abolished. References to a treatment that may "not abolish" plasma corticosterone levels may refer to retaining at least 0.01%, 0.1%, 1%, 2%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50% or more of the plasma corticosterone level prior to treatment (such as anti-ACTH administration). The systematic (IUPAC) name of corticosterone is (11β)-11,21-dihydroxypregn-4-ene-3,20-dione and its structure is well known in the art and is shown below:



[0226] The term "aldosterone" refers is a steroid hormone of the mineralocorticoid family which is produced by the outer section (zona glomerulosa) of the adrenal cortex in the adrenal gland which plays a role in the regulation of blood pressure. The systematic (IUPAC) name of aldosterone is 11β,21-Dihydroxy-3,20-dioxopregn-4-en-18-al and its structure is well known in the art and is shown below:



[0227] The terms "biological effects associated with ACTH" and "ACTH activity" are used interchangeably and include any biological effect of ACTH. In certain embodiments, ACTH activity includes the ability of ACTH to interact or bind to a receptor. In some embodiments, ACTH activity is represented by the ability of ACTH to bind to a melanocortin receptor (MCR). In some embodiments, ACTH binds to and activates MC2R in the adrenal cortex, thereby resulting in the production of cAMP, which activates PKA which in turn activates enzymes that convert cholesterol to cortisol, i.e., ACTH signaling through MC2R induces cortisol secretion. ACTH can also bind to MC1R, MC3R, MC4R and/or MC5R and induce other biological effects.

[0228] The term "condition associated with elevated ACTH levels" refers to any condition, disorder and disease present in a subject who also has elevated plasma ACTH levels. Elevated ACTH levels are often associated with elevated cortisol levels since ACTH is the primary stimulator of adrenal cortisol production. ACTH and cortisol levels exhibit peaks (6-8 a.m.) and nadirs (11 p.m.). Only a small percentage of circulating cortisol is biologically active (i.e., free form), with the majority of cortisol inactive (i.e., protein bound). Cortisol is inactivated in the liver and excreted in the urine as conjugated compounds (e.g., 17-hydroxysteroids). Urine free cortisol levels reflect circulating free plasma cortisol levels. Since blood tests alone may not detect the presence of excessive cortisol secretion (since levels naturally vary throughout the day), testing for elevated cortisol generally involves a combination of 24-hour urine free cortisol (UFC) measurement, cortisol saliva testing and blood tests. Measurement of ACTH levels, however, is most commonly achieved by blood testing. Typically, blood will be drawn in the morning to obtain a peak ACTH level and/or drawn in the evening to obtain a low (trough) ACTH level. Normal values for ACTH blood levels range from 9 - 52 pg/mL or 10-60 pg/mL for morning blood draws (there is no established reference value for evening blood draws). Higher than normal levels of ACTH may be present with hypertension, obstructive sleep apnea (OSA), adrenal hyperplasia, congenital adrenal hyperplasia, Cushing's Disease, or Cushing's Syndrome, and other diseases, disorders, and conditions.

[0229] As used herein, a "condition associated with ACTH" includes any disease, disorder, or condition that may be treated by antagonizing ACTH, for example by administration of an anti-ACTH antibody or antigen-binding fragment thereof according to the invention. Said disease, disorder, or condition may be characterized by elevated ACTH. Said disease, disorder, or condition may be characterized by changes in the level of a substance or in a biological process that can be ameliorated or reversed by antagonizing ACTH, including diseases, disorders, or conditions associated with elevated cortisol or aldosterone, wherein antagonism of ACTH may reduce said level of cortisol or aldosterone. Said diseases, disorders, or conditions include those associated with a symptom that can be ameliorated by antagonizing ACTH, whether or not ACTH is thought to play a causative role in the disease. Additional terms that are used interchangeably with "condition associated with ACTH" include "disease associated with ACTH" as well as the terms "ACTH-related", "ACTH-induced",

"ACTH-driven", "ACTH-mediated" and "ACTH-associated" when used in the context of diseases, disorders, or conditions. Examples of conditions associated with ACTH include, without limitation thereto, ACTH-driven hypercortisolism, acute coronary syndrome, acute heart failure, Alzheimer's disease, anxiety disorders, atherosclerosis, atrial fibrillation, cachexia, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), cardiac conditions, cardiac fibrosis, cardiovascular disorders, chronic renal failure, chronic stress syndrome, cognitive dysfunction, congestive heart failure, Conn's syndrome, coronary heart diseases, Cushing's Disease, Cushing's Syndrome, depression, diabetes, endothelial dysfunction, exercise intolerance, familial hyperaldosteronism, fibrosis, galactorrhea, heart failure, hyperaldosteronism, hypercortisolemia, hypertension, hypokalemia, impaired cardiac function, increased formation of collagen, inflammation, metabolic syndrome, muscle atrophy, conditions associated with muscle atrophy, myocardiac fibrosis, nephropathy, obesity, post-myocardial infarction, primary hyperaldosteronism, remodeling following hypertension, renal failure, restenosis, secondary hyperaldosteronism, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), and syndrome X. Said condition associated with ACTH may be treated in a human, or in a non-human animal such as dog, cat, or horse, or another animal species.

[0230] The term "condition associated with elevated cortisol, corticosterone and/or aldosterone levels" refers to any condition, disorder and disease present in a subject who also has elevated plasma cortisol, corticosterone and/or aldosterone levels. Elevated aldosterone levels or hyperaldosteronism are associated with conditions such as primary hyperaldosteronism (including Conn's syndrome), secondary hyperaldosteronism, and familial hyperaldosteronism. Elevated cortisol levels, for example, are often associated with conditions such as anxiety disorders, stress, depression, obesity, cancer, muscle atrophy, hypertension, heart failures, diabetes, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), hyperinsulinemia, Alzheimer's disease, dementia and other cognitive dysfunction, galactorrhea, metabolic syndrome, congenital adrenal hyperplasia, Cushing's Syndrome and Cushing's Disease. Familial hyperaldosteronism includes a group of related heritable conditions that result in excessive production of aldosterone. Familial hyperaldosteronism patients often exhibit severe hypertension, and may exhibit enlarged adrenal glands. Familial hyperaldosteronism can be categorized into three types, distinguished by their clinical features and genetic causes. In familial hyperaldosteronism type I, hypertension generally appears in childhood to early adulthood and can range from mild to severe. This type can be treated with steroid medications called glucocorticoids, so it is also known as glucocorticoid-remediable aldosteronism (GRA). One known genetic cause of familial hyperaldosteronism type I is the fusion the genes *CYP11B1* and *CYP11B2*, which are located close together on chromosome 8. In familial hyperaldosteronism type II, hypertension usually appears in early to middle adulthood and does not improve with glucocorticoid treatment. In most

individuals with familial hyperaldosteronism type III, the adrenal glands are enlarged up to six times their normal size. These affected individuals have severe hypertension that starts in childhood. The hypertension is difficult to treat and often results in damage to organs such as the heart and kidneys. Rarely, individuals with type III have milder symptoms with treatable hypertension and no adrenal gland enlargement. Familial hyperaldosteronism type III can be caused by mutations in the *KCNJ5* gene which encodes a potassium channel.

[0231] The term "Cushing's disease" refers to a serious condition of an excess level of the steroid hormone cortisol in the blood caused by a pituitary tumor secreting ACTH. Cushing's disease is rare, affecting 10 to 15 people per million each year, most commonly adults between 20 and 50 years of age. Women account for more than 70 percent of cases. Most subjects with Cushing's disease have small tumors (pituitary microadenomas). Cushing's disease is used exclusively to describe the condition of excessive cortisol arising from a pituitary tumor secreting the hormone ACTH. Magnetic resonance imaging (MRI) scan of the pituitary gland is the best way to detect the presence of an adenoma in Cushing's disease. MRI detects a pituitary adenoma in about 70 percent of cases. In the event that MRI scan fails to detect an abnormality despite indications of Cushing's disease via clinical findings and hormonal testing, inferior petrosal sinus sampling (IPSS) may be used to assess the ACTH levels in the inferior petrosal sinus compared to a vein just below the heart. In Cushing's disease, the ACTH level in the inferior petrosal sinus is much higher compared to the vein below the heart.

[0232] Cushing's disease is not the same as Cushing's Syndrome. The term "Cushing's Syndrome" refers to the general state characterized by excessive levels of cortisol in the blood. Elevated cortisol levels can occur for reasons other than a pituitary tumor, including, e.g., tumors of the adrenal glands producing cortisol; and ectopic ACTH production (i.e., certain types of cancer, elsewhere in the body, can make ACTH, which then stimulates the normal adrenal glands to make excessive cortisol). Cushing's Syndrome resulting from ectopic ACTH expression is frequently cause by neoplasms including small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors (such as gliomas, neuroepitheliomatous tumors, or nerve sheath tumors) and thymoma. Small cell lung cancer is a particularly prominent as it has been observed to account for up to 50% of Cushing's Syndrome of ectopic or neoplastic origin.

[0233] Cushing's Syndrome is much more common than Cushing's disease. The most common cause of elevated cortisol levels is taking medications that have cortisol, including, but not limited to, hydrocortisone, prednisone pills, skin ointments, asthma inhalers and joint steroid injections. Other, albeit less common, causes of elevated cortisol levels include, for example, an adrenal tumor or "Pseudo-Cushing's" (i.e., chronically elevated levels of cortisol due to, e.g., depression, alcohol abuse, anorexia nervosa or high estrogen levels).

[0234] The term "sleep disorder" means any condition associated with irregular sleep patterns, e.g., sleep apnea, insomnia, hypersomnia, narcolepsy and other dyssomnias.

[0235] The term "sleep apnea" refers to a potentially serious sleep disorder in which breathing repeatedly stops and starts. There are two main types of sleep apnea: (1) obstructive sleep apnea (OSA), which is the more common form, that occurs when throat muscles relax; and (2) central sleep apnea (CSA), which occurs when your brain doesn't send proper signals to the muscles that control breathing. OSA occurs when the muscles in the back of the throat, which support the soft palate, the uvula, the tonsils, the side walls of the throat and the tongue, relax such that the airway narrows or closes preventing an adequate breath in. This may lower the level of oxygen in your blood. The brain senses the inability to breathe and briefly rouses a person from sleep in order to reopen the airway. The awakening is usually so brief that it is not remembered. In fact, a person with OSA may not be aware that their sleep was disrupted, i.e., some people with this type of sleep apnea think they sleep well all night. A person may also make a snorting, choking or gasping sound. The pattern of sleep/awake can repeat itself, e.g., 5 to 30 times or more each hour, all night. These disruptions impair the ability to reach the desired deep, restful phases of sleep, and often result in a person suffering from OSA feeling sleepy during their waking hours. CSA, which is much less common than OSA, occurs when the brain fails to transmit signals to the breathing muscles. A person with CSA may awaken with shortness of breath and/or have a difficult time getting to sleep or staying asleep. As with OSA, snoring and daytime sleepiness can occur. The most common cause of CSA is heart failure and, less commonly, a stroke. People with CSA may be more likely to remember awakening than are people with OSA.

[0236] The signs and symptoms of OSA and CSA can overlap, which makes it difficult to identify the type of sleep apnea. The most common signs and symptoms of obstructive and central sleep apneas include: excessive daytime sleepiness (hypersomnia); loud snoring (usually more prominent in OSA); episodes of breathing cessation during sleep witnessed by another person; abrupt awakenings accompanied by shortness of breath (more likely indicates CSA); awakening with a dry mouth or sore throat; morning headache; difficulty staying asleep (insomnia); and/or attention problems.

[0237] Although sleep apnea can affect anyone, including children, there are certain factors associated with an increased risk of sleep apnea. Risk factors for OSA include, but are not limited to, excess weight (i.e., fat deposits around your upper airway may obstruct your breathing); neck circumference (i.e., people with a thicker neck may have a narrower airway; a narrowed airway (i.e., a naturally narrow throat and/or enlarged tonsils or adenoids); gender (i.e., men are twice as likely as woman to develop sleep apnea, although a woman's risk is increased if she is overweight and/or post-menopausal); age (i.e., sleep apnea occurs significantly more often in adults older than 60); family history (i.e., increased risk for individuals who have family members with sleep apnea); race (i.e., in people under 35 years old, people of African descent are more likely to have obstructive sleep apnea);

use of alcohol, sedatives or tranquilizers which relax the muscles in your throat; smoking (i.e., smokers are three times more likely to have OSA than non-smokers due to, e.g., increased inflammation and fluid retention in the upper airway); nasal congestion (i.e., difficulty breathing through your nose, e.g., whether an anatomical problem or allergies, is associated with increased likelihood of developing OSA). Risk factors for CSA include, but are not limited to, gender (i.e., males at increased risk); age (i.e., people over 65 years of age have a higher risk of CSA); heart disorders (i.e., people with atrial fibrillation or congestive heart failure are more at risk of CSA); and stroke or brain tumor (i.e., these conditions can impair the brain's ability to regulate breathing.

[0238] Sleep apnea is considered a serious medical condition with complications including, but not limited to, high blood pressure (i.e., hypertension) and heart problems, daytime fatigue, depression, behavioral problems, problems with medications and/or surgery, liver problems and sleep-deprived partners.

[0239] "About" where used means especially ± 10%, ± 5% or ± 3% (referring to the given numeric value, respectively), if not indicated otherwise. In each of the invention embodiments, "about" can be deleted.

[0240] The term "host cell" herein in general refers to any cell engineered to express one or more antibody polypeptides according to the invention. This includes by way of example bacterial, fungal, yeast, mammalian, invertebrate such as insect, plant and avian cells. Preferred host cells are yeast, fungi, especially filamentous fungi and mammalian cells. Yeast and filamentous fungi include, but are not limited to *Pichia pastoris*, *Pichia finlandica*, *Pichia trehalophila*, *Pichia koclamae*, *Pichia membranaefaciens*, *Pichia minuta (Ogataea minuta, Pichia lindneri)*, *Pichia opuntiae*, *Pichia thermotolerans*, *Pichia salictaria*, *Pichia guercuum*, *Pichia pijperi*, *Pichia stiptis*, *Pichia methanolica*, *Pichia sp.*, *Saccharomyces cerevisiae*, *Saccharomyces sp.*, *Hansenula polymorpha*, *Kluyveromyces sp.*, *Kluyveromyces lactis*, *Candida albicans*, *Aspergillus nidulans*, *Aspergillus niger*, *Aspergillus oryzae*, *Trichoderma reesei*, *Chrysosporium lucknowense*, *Fusarium sp.*, *Fusarium gramineum*, *Fusarium venenatum*, *Physcomitrella patens* and *Neurospora crassa. Pichia sp.*, any *Saccharomyces sp.*, *Hansenula polymorpha*, any *Kluyveromyces sp.*, *Candida albicans*, any *Aspergillus sp.*, *Trichoderma reesei*, *Chrysosporium lucknowense*, any *Fusarium sp.* and *Neurospora crassa.*

[0241] Examples of invertebrate cells include insect cells such as Drosophila S2 and Spodoptera Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., *J. Gen Virol.*, 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, *PNAS USA*, 77:4216 (1980)); mouse Sertoli cells (TM4, Mather, *Biol. Reprod.*, 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection

of the appropriate host cell is deemed to be within the skill in the art. Preferred mammalian cells for antibody expression include CHO cells and COS cells. In an exemplary embodiment the recombinant host cells are polyploid yeast cells of the genus *Pichia*.

[0242] *Mating competent yeast species*: In the present invention this is intended to broadly encompass any diploid or tetraploid yeast which can be grown in culture. Such species of yeast may exist in a haploid, diploid, or other polyploid form. The cells of a given ploidy may, under appropriate conditions, proliferate for an indefinite number of generations in that form. Diploid cells can also sporulate to form haploid cells. Sequential mating can result in tetraploid strains through further mating or fusion of diploid strains. The present invention contemplates the use of haploid yeast, as well as diploid or other polyploid yeast cells produced, for example, by mating or spheroplast fusion.

[0243] Mating competent yeast include yeast which are a member of the *Saccharomycetaceae* family, which includes the genera *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*. Other types of yeast potentially useful in the invention include *Yarrowia*; *Rhodosporidium*; *Candida*; *Hansenula*; *Filobasium*; *Sporidiobolus*; *Bullera*; *Leucosporidium* and *Filobasidella*.

[0244] In a preferred embodiment of the invention, the mating competent yeast is a member of the genus *Pichia*. In a further preferred embodiment of the invention, the mating competent yeast of the genus *Pichia* is one of the following species: *Pichia pastoris*, *Pichia methanolica*, and *Hansenula polymorpha* (*Pichia angusta*). In a particularly preferred embodiment of the invention, the mating competent yeast of the genus *Pichia* is the species *Pichia pastoris*.

[0245] *Haploid Yeast Cell*: A cell having a single copy of each gene of its normal genomic (chromosomal) complement.

[0246] *Polyploid Yeast Cell*: A cell having more than one copy of its normal genomic (chromosomal) complement.

[0247] *Diploid Yeast Cell*: A cell having two copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (mating) of two haploid cells.

[0248] *Tetraploid Yeast Cell*: A cell having four copies (alleles) of essentially every gene of its normal genomic complement, typically formed by the process of fusion (mating) of two haploid cells. Tetraploids may carry two, three, four or more different expression cassettes. Such tetraploids might be obtained in *S. cerevisiae* by selective mating homozygotic heterothallic a/a and alpha/alpha diploids and in *Pichia* by sequential mating of haploids to obtain auxotrophic diploids. For example, a [met his] haploid can be mated with [ade his] haploid to obtain diploid [his]; and a [met arg] haploid can be mated with [ade arg] haploid to obtain diploid [arg]; then the diploid [his] x diploid [arg] to

obtain a tetraploid prototroph. It will be understood by those of skill in the art that reference to the benefits and uses of diploid cells may also apply to tetraploid cells.

[0249] *Yeast Mating*: The process by which two haploid yeast cells naturally fuse to form one diploid yeast cell.

[0250] *Meiosis*: The process by which a diploid yeast cell undergoes reductive division to form four haploid spore products. Each spore may then germinate and form a haploid vegetatively growing cell line.

[0251] *Selectable Marker*: A selectable marker is a gene or gene fragment that confers a growth phenotype (physical growth characteristic) on a cell receiving that gene as, for example through a transformation event. The selectable marker allows that cell to survive and grow in a selective growth medium under conditions in which cells that do not receive that selectable marker gene cannot grow. Selectable marker genes generally fall into several types, including positive selectable marker genes such as a gene that confers on a cell resistance to an antibiotic or other drug, temperature when two temperature sensitive ("ts") mutants are crossed or a ts mutant is transformed; negative selectable marker genes such as a biosynthetic gene that confers on a cell the ability to grow in a medium without a specific nutrient needed by all cells that do not have that biosynthetic gene, or a mutagenized biosynthetic gene that confers on a cell inability to grow by cells that do not have the wild type gene; and the like. Suitable markers include but are not limited to: ZEO; G418; LYS3; MET1; MET3a; ADE1; ADE3; URA3; and the like.

[0252] *Expression Vector*: These DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host, *e.g. E. coli,* and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Stearns, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

[0253] Expression vectors for use in the methods of the invention will further include yeast specific sequences, including a selectable auxotrophic or drug marker for identifying transformed yeast strains. A drug marker may further be used to amplify copy number of the vector in a yeast host cell.

[0254] The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in yeast cells. These vector components may include, but are not limited to, one or more of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be included, e.g. a signal sequence, and the like. A yeast origin of replication is optional, as expression vectors are often integrated into the yeast genome. In one embodiment of the invention, the polypeptide of interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

[0255] Nucleic acids are "operably linked" when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (Gateway Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0256] Promoters are untranslated sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, *e.g.*, the presence or absence of a nutrient or a change in temperature.

[0257] The promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the host genome; alternatively a selectable marker is used as the site for homologous recombination.

[0258] Examples of suitable promoters useful in *Pichia* include the AOX1 promoter (Cregg *et al.* (1989) *Mol. Cell. Biol.* 9:1316-1323); ICL1 promoter (Menendez *et al.* (2003) *Yeast* 20(13):1097-108); glyceraldehyde-3-phosphate dehydrogenase promoter (GAP) (Waterham *et al.* (1997) *Gene* 186(1):37-44); and FLD1 promoter (Shen *et al.* (1998) *Gene* 216(1):93-102). The *GAP* promoter is a strong constitutive promoter and the AOX and FLD1 promoters are inducible.

[0259] Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and chimeric promoters derived therefrom. Additionally, non-yeast promoters may be used in the invention such as mammalian, insect, plant, reptile, amphibian, bacterial, fungal, viral, and avian

promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

[0260] The polypeptides of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, *e.g.* a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The *S. cerevisiae* alpha factor pre-pro signal has proven effective in the secretion of a variety of recombinant proteins from *P. pastoris*. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be engineered to provide for enhanced secretion in diploid yeast expression systems. Other secretion signals of interest also include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, *e.g.*, K28 preprotoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences, human Ig heavy chain, human Ig light chain, and the like. For example, see Hashimoto *et. al., Protein Eng* 11(2) 75 (1998); and Kobayashi *et. al., Therapeutic Apheresis* 2(4) 257 (1998).

[0261] Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to 300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5' and 3' to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5' or 3' to the coding sequence, but is preferably located at a site 5' from the promoter.

[0262] Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3' to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

[0263] Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and re-ligated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the

ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

[0264] As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) *Ann. Rev. Biochem. 58*:913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and *E. coli* –encoded recombination proteins. Recombination occurs between specific attachment (*att*) sites on the interacting DNA molecules. For a description of att sites see Weisberg and Landy (1983) Site-Specific Recombination in Phage Lambda, in *Lambda II*, Weisberg, ed.(Cold Spring Harbor, NY:Cold Spring Harbor Press), pp. 211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the *att* sites are hybrid sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

[0265] *Att* sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing *att* B sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing att sites; and the like.

[0266] *Folding*, as used herein, refers to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. While non-covalent interactions are important in determining structure, usually the proteins of interest will have intra- and/or intermolecular covalent disulfide bonds formed by two cysteine residues. For naturally occurring proteins and polypeptides or derivatives and variants thereof, the proper folding is typically the arrangement that results in optimal biological activity, and can conveniently be monitored by assays for activity, *e.g.* ligand binding, enzymatic activity, *etc.*

[0267] In some instances, for example where the desired product is of synthetic origin, assays based on biological activity will be less meaningful. The proper folding of such molecules may be determined on the basis of physical properties, energetic considerations, modeling studies, and the like.

[0268] The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, *i.e.* foldases, chaperonins, *etc.* Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, *etc.* as known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

[0269] For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond isomerization, but also exhibits chaperone activity. Co-expression of

PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin; and the like. In one embodiment of the invention, each of the haploid parental strains expresses a distinct folding enzyme, *e.g.* one strain may express BIP, and the other strain may express PDI or combinations thereof.

[0270] The terms "*desired protein*" or "*desired antibody*" are used interchangeably and refer generally to a parent antibody or fragment specific to a target, i.e., ACTH or a chimeric or humanized antibody or a binding portion thereof derived therefrom or one containing the same CDRs or epitopic specificity as any of the anti-ACTH antibodies or fragments described herein. The term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be "antibodies." A preferred source for producing antibodies useful as starting material according to the invention is rabbits. Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the art. Examples thereof include chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies (such as scFvs), camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments such as Fabs, Fab', $F(ab')_2$, monovalent antibody fragments such as MetMab like molecules, and the like. See Streltsov VA, et al., Structure of a shark IgNAR antibody variable domain and modeling of an early-developmental isotype, *Protein Sci.* 2005 Nov;14(11):2901-9. Epub 2005 Sep 30; Greenberg AS, et al., A new antigen receptor gene family that undergoes rearrangement and extensive somatic diversification in sharks, *Nature.* 1995 Mar 9;374(6518):168-73; Nuttall SD, et al., Isolation of the new antigen receptor from wobbegong sharks, and use as a scaffold for the display of protein loop libraries, Mol Immunol. 2001 Aug;38(4):313-26; Hamers-Casterman C, et al., Naturally occurring antibodies devoid of light chains, *Nature.* 1993 Jun 3;363(6428):446-8; Gill DS, et al., Biopharmaceutical drug discovery using novel protein scaffolds, *Curr Opin Biotechnol.* 2006 Dec;17(6):653-8. Epub 2006 Oct 19.

[0271] The present invention includes in particular includes monovalent antibody molecules that bind ACTH, which are analogous to MetMab molecules. MetMab is a monovalent antibody specific to Met. (Met is a protein encoded by the nucleotide sequence set forth in Park et al., *PNAS USA* 84, 6379-83 (1987), or fragments thereof, as well as related polypeptides, which include, but are not limited to, allelic variants, splice variants, derivative variants, substitution variants, deletion variants, and/or insertion variants, fusion polypeptides, and interspecies homologs). The MetMab antibody, is a

monovalent antibody known by different names including OA-5d5 (Genentech) and is also called One Armed 5d5, 5d5, MetMab, PRO143966, among others). Antibody OA-5d5, including its structure and properties, and methods for making and using it, are described in U.S. Publication No. 2007/0092520. In one embodiment, an anti-ACTH antibody according to the invention may comprise a single Fab region linked to an Fc region. In such embodiment, an antibody of the invention may comprise light and heavy chain variable domains as described herein. In such an embodiment, the antibody is monovalent and may comprise an intact Fc region. In another such embodiment, the Fc region may comprise at least one protuberance (knob) and at least one cavity (hole), wherein the presence of the protuberance and cavity enhances formation of a complex between an Fc polypeptide comprising the protuberance and an Fc polypeptide comprising the cavity, for example as described in WO 2005/063816. In one embodiment, the Fc region of an antibody of the invention may comprise a first and a second Fc polypeptide, wherein the first and second polypeptide each comprises one or more mutations with respect to wild type human Fc. In one embodiment, a cavity mutation is T366S, L368A and/or Y407V. In another embodiment, a protuberance mutation is T366W. In a specific embodiment, a monovalent antibody according to the subject invention may comprise a one-armed antibody synthesized as described in WO2005/063816. In such embodiment, the one-armed antibody may comprise Fc mutations constituting "knobs" and "holes" as described in WO2005/063816. For example, a hole mutation can be one or more of T366A, L368A and/or Y407V in an Fc polypeptide, and a cavity mutation can be T366W. The invention is also directed to an anti-human ACTH monovalent agent that binds with the same ACTH epitope and/or competes with an anti-ACTH antibody for binding to ACTH as an antibody or antibody fragment disclosed herein.

[0272] For example, antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

[0273] Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa)

substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of one or more cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (*e.g.*, a functional domain, catalytic amino acid residues, *etc*). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Techniques for *in vitro* mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.

[0274] As used herein, the terms "chimeric antibodies" and "chimerized antibodies" (as well as the respective singular forms thereof) are used interchangeably and have the same meaning. Chimeric antibodies generally comprise one or more variable domains of one species origin and a constant domain of another species origin. Most typically a chimeric antibody comprises variable heavy and variable light chain antibodies of non-human (e.g., rabbit, or rodent) one or both of which are linked to a constant domain of another species origin (e.g., human). Exemplary chimeric antibodies comprise a variable heavy chain of rabbit origin linked (e.g., fused) to a constant heavy chain of human origin (such as the heavy chain constant domain polypeptide of SEQ ID NO: 886, 887, or 888), and may further contain a variable light chain of rabbit origin which may be linked (e.g., fused) to a light chain of human origin (or rabbit origin).

[0275] Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions (V_L and V_H), obtained from antibody producing cells of one species with the constant light and heavy chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, e.g., in U.S. Patent No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, and IgG4 constant regions.

[0276] Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate primarily the complementarity-determining regions of the animal-derived antibody. This is accomplished by carefully examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and grafting them to the human antibody frameworks that are most similar to the rabbit sequence present in the particular antibody. This can also be

achieved by fitting the CDRs to the structure of the human antibody chains. See, e.g., U.S. Patent No. 6,187,287, incorporated fully herein by reference.

[0277] In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab', $F(ab')_2$, Fab, or other fragments) may be synthesized. "Fragment" or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable heavy chain region. Combinations of antibodies are also of interest, *e.g.* diabodies, which comprise two distinct Fv specificities. In another embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

[0278] Immunoglobulins and fragments thereof may be modified post-translationally, *e.g.* to add effector moieties such as chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. Examples of additional effector molecules are provided *infra*.

[0279] A polynucleotide sequence "corresponds" to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (i.e., the polynucleotide sequence "encodes" the polypeptide sequence), one polynucleotide sequence "corresponds" to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

[0280] A "heterologous" region or domain of a DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a heterologous region is a construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

[0281] A "coding sequence" is an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A "promoter sequence" is a DNA regulatory region

capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for binding of regulatory molecules (e.g., transcription factors) which affect the transcription of the coding sequence. A coding sequence is "under the control" of the promoter sequence or "operatively linked" to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence.

[0282] Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for polynucleotides) and liposomes (for polypeptides). A "DNA vector" is a replicon, such as plasmid, phage or cosmid, to which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An "expression vector" is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell. This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypeptide encoded by said polynucleotide sequence.

[0283] "Amplification" of polynucleotide sequences is the *in vitro* production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in the form of DNA. A variety of techniques for carrying out such amplification are described in a review article by Van Brunt (1990, Bio/Technol., 8(4):291-294). Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

[0284] The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., Ann. N.Y. Acad. Sci., 190: 5 (1971)). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 25,000 Daltons (the "light chain"), and two identical heavy chains of molecular weight approximately 50,000 Daltons (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" configuration. The "branch" portion of the "Y" configuration is designated the F_{ab} region; the stem portion of the "Y" configuration is designated the F_C region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y" configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

[0285] The variable region is linked in each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (i.e., the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE corresponding to γ, μ, α, δ, and ε (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A., Structural Concepts in Immunology and Immunochemistry, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., *et al.*, Clinical Immunobiology, pp 1-18, W. B. Sanders (1980); Kohl, S., *et al.*, Immunology, 48: 187 (1983)); while the variable region determines the antigen with which it will react. Light chains are classified as either κ (kappa) or λ (lambda). Each heavy chain class can be prepared with either kappa or lambda light chain. The light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

[0286] The expression "variable region" or "VR" refers to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain (V_L) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0287] The expressions "complementarity determining region," "hypervariable region," or "CDR" refer to one or more of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (*See* Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat *et al.* ("Sequences of Proteins of Immunological Interest," Kabat E., *et al.*, US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, J Mol. Biol. 196 901-917 (1987)). The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the antibody-antigen interaction (Kashmiri, S., Methods, 36:25-34 (2005)).

[0288] An "epitope" or "binding site" is an area or region on an antigen to which an antigen-binding peptide (such as an antibody) specifically binds. A protein epitope may comprise amino acid residues directly involved in the binding (also called immunodominant component of the epitope) and other amino acid residues, which are not directly involved in the binding, such as amino acid residues

which are effectively blocked by the specifically antigen binding peptide (in other words, the amino acid residue is within the "footprint" of the specifically antigen binding peptide). The term epitope herein includes both types of amino acid binding sites in any particular region of ACTH that specifically binds to an anti-ACTH antibody. ACTH may comprise a number of different epitopes, which may include, without limitation, (1) linear peptide antigenic determinants, (2) conformational antigenic determinants which consist of one or more non-contiguous amino acids located near each other in a mature ACTH conformation; and (3) post-translational antigenic determinants which consist, either in whole or part, of molecular structures covalently attached to an ACTH protein such as carbohydrate groups.

[0289] The phrase that a first antibody binds "substantially" or "at least partially" the same epitope as a second antibody means that the epitope binding site for the first antibody comprises at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more of the amino acid residues on the antigen that constitutes the epitope binding site of the second antibody. Also, that a first antibody binds substantially or partially the same or overlapping epitope as a second antibody means that the first and second antibodies compete in binding to the antigen, as described above. Thus, the term "binds to substantially the same epitope or determinant as" a monoclonal antibody means that an antibody "competes" with the antibody.

[0290] The phrase "binds to the same or overlapping epitope or determinant as" an antibody of interest means that an antibody "competes" with said antibody of interest for at least one, (e.g., at least 2, at least 3, at least 4, at least 5) or all residues on ACTH to which said antibody of interest specifically binds. The identification of one or more antibodies that bind(s) to substantially or essentially the same epitope as the monoclonal antibodies described herein can be readily determined using alanine scanning. Additionally, any one of variety of immunological screening assays in which antibody competition can be assessed. A number of such assays are routinely practiced and well known in the art (see, e.g., U.S. Pat. No. 5,660,827, issued Aug. 26, 1997, which is specifically incorporated herein by reference). It will be understood that actually determining the epitope to which an antibody described herein binds is not in any way required to identify an antibody that binds to the same or substantially the same or overlapping epitope as the monoclonal antibody described herein.

[0291] For example, where the test antibodies to be examined are obtained from different source animals, or are even of a different Ig isotype, a simple competition assay may be employed in which the control antibody is mixed with the test antibody and then applied to a sample containing ACTH. Protocols based upon ELISAs, radioimmunoassays, Western blotting, and the use of BIAcore® analysis are suitable for use in such simple competition studies.

[0292] In certain embodiments, one would pre-mix the control anti-ACTH antibody with varying amounts of the test antibody (e.g., in ratios of about 1:1, 1:2, 1:10 or about 1:100) for a period of time prior to applying to the ACTH antigen sample. In other embodiments, the control and varying

amounts of test antibody can simply be added separately and admixed during exposure to the ACTH antigen sample. As long as one can distinguish bound from free antibodies (e.g., by using separation or washing techniques to eliminate unbound antibodies) and control antibody from the test antibody (e.g., by using species specific or isotype specific secondary antibodies or by specifically labeling the control antibody with a detectable label) one will be able to determine if the test antibody reduces the binding of the control antibody to the ACTH antigens, indicating that the test antibody recognizes substantially the same epitope as the control anti-ACTH antibody. The binding of the (labeled) control antibody in the presence of a completely irrelevant antibody (that does not bind ACTH) can serve as the control high value. The control low value can be obtained by incubating the labeled control antibody with the same but unlabeled control antibody, where competition would occur and reduce binding of the labeled antibody. In a test assay, a significant reduction in labeled antibody reactivity in the presence of a test antibody is indicative of a test antibody that recognizes substantially the same epitope, i.e., one that competes with the labeled control antibody. For example, any test antibody that reduces the binding of the control antibody to ACTH by at least about 50%, such as at least about 60%, or more preferably at least about 70% (e.g., about 65%-100%), at any ratio of test antibody between about 1:1 or 1:10 and about 1:100 is considered to be an antibody that binds to substantially the same or overlapping epitope or determinant as the control antibody.

[0293] Preferably, such test antibody will reduce the binding of the control antibody to ACTH antigen preferably at least about 50%, at least about 60%, at least about 80% or at least about 90% (e.g., about 95%) of the binding of the control antibody observed in the absence of the test antibody.

[0294] A simple competition assay in which a test antibody is pre-adsorbed and applied at saturating concentration to a surface onto which ACTH is immobilized also may be advantageously employed. The surface in the simple competition assay is preferably a BIAcore® chip (or other media suitable for surface plasmon resonance analysis). The binding of a control antibody that binds ACTH to the ACTH-coated surface is measured. This binding to the ACTH-containing surface of the control antibody alone is compared with the binding of the control antibody in the presence of a test antibody. A significant reduction in binding to the ACTH-containing surface by the control antibody in the presence of a test antibody indicates that the test antibody recognizes substantially the same epitope as the control antibody such that the test antibody "competes" with the control antibody. Any test antibody that reduces the binding of control antibody by at least about 20% or more, at least about 40%, at least about 50%, at least about 70%, or more, can be considered to be an antibody that binds to substantially the same epitope or determinant as the control antibody. Preferably, such test antibody will reduce the binding of the control antibody to ACTH by at least about 50% (e.g., at least about 60%, at least about 70%, or more). It will be appreciated that the order of control and test antibodies can be reversed; i.e. the control antibody can be first bound to the surface and then the test antibody is brought into contact with the surface thereafter in a competition assay. Preferably, the

antibody having greater affinity for ACTH antigen is bound to the ACTH-containing surface first, as it will be expected that the decrease in binding seen for the second antibody (assuming the antibodies are competing) will be of greater magnitude. Further examples of such assays are provided in e.g., Saunal and Regenmortel, (1995) *J. Immunol. Methods* 183: 33-41, the disclosure of which is incorporated herein by reference.

[0295] In addition, whether an antibody binds the same or overlapping epitope(s) on ACTH as another antibody or the epitope bound by a test antibody may in particular be determined using a western-blot based assay. In this assay a library of peptides corresponding to the antigen bound by the antibody, herein ACTH is made, which correspond to overlapping portions of the protein, typically 10-25, 10-20 or 10-15 amino acids long. These different overlapping amino acid peptides encompassing the ACTH sequence are synthesized and covalently bound to a PepSpots nitrocellulose membrane (JPT Peptide technologies, Berlin, Germany). Blots are then prepared and probed according to the manufacturer's recommendations.

[0296] Essentially, the immunoblot assay then detects by fluorometric means what peptides in the library bind to the test antibody and thereby can identify what residues on the antigen, i.e., ACTH, interact with the test antibody. (See an embodiment of this technique in US Patent No. 7,935,340, incorporated by reference herein).

[0297] The expressions "framework region" or "FR" refer to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody (*See* Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody.

[0298] ***Anti-ACTH Antibodies and Binding Fragments Thereof Having Binding Activity for ACTH***

[0299] Adrenocorticotropic hormone (ACTH), also known as corticotropin, is a polypeptide tropic hormone produced and secreted by the anterior pituitary gland. It is an important component of the hypothalamic-pituitary-adrenal axis and is often produced in response to biological stress (along with its precursor corticotropin-releasing hormone from the hypothalamus). Its principal effects are increased production and release of corticosteroids. When a pituitary tumor is the cause of elevated ACTH (from the anterior pituitary) this is known as Cushing's Disease and the constellation of signs and symptoms of the excess cortisol (hypercortisolism) is known as Cushing's Syndrome. A deficiency of ACTH is a cause of secondary adrenal insufficiency. ACTH is also related to the circadian rhythm in many organisms. Moreover, elevated ACTH and cortisol production have been associated with sleep apnea, particularly OSA. See Henley et al., J Clin Endocrinol Metab. November 2009, 94(11):4234–4242.

[0300] POMC, ACTH and β-lipotropin are secreted from corticotropes in the anterior lobe (or adenohypophysis) of the pituitary gland in response to the hormone corticotropin-releasing hormone (CRH) released by the hypothalamus. ACTH is synthesized from pre-pro-opiomelanocortin (pre-POMC). The removal of the signal peptide during translation produces the 241-amino acid polypeptide POMC, which undergoes a series of post-translational modifications such as phosphorylation and glycosylation before it is proteolytically cleaved by endopeptidases to yield various polypeptide fragments with varying physiological activity.

[0301] ACTH consists of 39 amino acids and can be processed into two shorter peptides, α-melanocyte-stimulating hormone (α-MSH) and CLIP. Alpha-MSH consists of amino acids 1-13 of human ACTH and CLIP consists of amino acids 18-39 of human ACTH. Human ACTH has a molecular weight of 4,540 atomic mass units (Da).

[0302] ACTH stimulates secretion of glucocorticoid steroid hormones from adrenal cortex cells, especially in the zona fasciculata of the adrenal glands. ACTH acts by binding to cell surface ACTH receptors, e.g., MC2R, which are located primarily on adrenocortical cells of the adrenal cortex. The ACTH receptor is a seven-membrane-spanning G protein-coupled receptor. Upon ligand binding, the receptor undergoes conformation changes that stimulate the enzyme adenylyl cyclase, which leads to an increase in intracellular cAMP and subsequent activation of protein kinase A.

[0303] ACTH influences steroid hormone secretion by both rapid short-term mechanisms that take place within minutes and slower long-term actions. The rapid actions of ACTH include stimulation of cholesterol delivery to the mitochondria where the P450scc enzyme is located. P450scc catalyzes the first step of steroidogenesis that is cleavage of the side-chain of cholesterol. ACTH also stimulates lipoprotein uptake into cortical cells. This increases the bio-availability of cholesterol in the cells of the adrenal cortex.

[0304] The long term actions of ACTH include stimulation of the transcription of the genes coding for steroidogenic enzymes, especially P450scc, steroid 11β-hydroxylase, and their associated electron transfer proteins. This effect is observed over several hours.

[0305] The present invention provides novel antibodies or antibody fragments that bind ACTH, including human ACTH. In preferred embodiments, the antibody or antibody fragment according to the invention comprises one or more complementarity determining regions (CDRs) of the anti-ACTH antibodies and antibody fragments described herein.

[0306] In some embodiments, an anti-ACTH antibody or antibody fragment according to the invention will interfere with, block, reduce or modulate the interaction between ACTH and MCRs (e.g., MC1R, MC2R, MC3R, MC4R and/or MC5R). In some instances an anti-ACTH antibody or antibody fragment according to the invention is denoted as "neutralizing", e.g., if it totally prevents the interaction of ACTH and MCR. In some embodiments, the antibody or antibody fragment neutralizes ACTH, e.g., by remaining bound to ACTH in a location and/or manner that prevents

ACTH from binding to MCRs. This in turn results in a reduction in the amount of serum cortisol present in a subject.

[0307] In some embodiments, the antibody or antibody fragment according to the invention are capable of inhibiting ACTH-mediated activity (including binding). In some embodiments, the antibody or antibody fragment according to the invention are humanized, such as humanized rabbit antibodies to ACTH.

[0308] As mentioned, the anti-ACTH antibodies or antibody fragments according to the invention have a variety of utilities. For example, the subject antibodies and fragments are useful in therapeutic applications, as well as diagnostically in binding assays, and are useful for affinity purification of ACTH, in particular human ACTH or its ligands and in screening assays to identify other antagonists of ACTH activity. Some of the antibodies or antibody fragments according to the invention are useful for inhibiting binding of ACTH to MCRs, or inhibiting ACTH-mediated activities.

[0309] The antibody or antibody fragment according to the invention can be used in a variety of therapeutic applications. For example, in some embodiments the anti-ACTH antibody or antibody fragment according to the invention are useful for treating conditions associated with ACTH, such as Cushing's Disease, Cushing's Syndrome, obesity, diabetes, depression, anxiety disorders, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), muscle atrophy, hypertension, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), hyperinsulinemia, cognitive dysfunction, Alzheimer's disease, galactorrhea, stress related conditions, impaired cardiac function, exercise intolerance, heart failure and other cardiac conditions, metabolic syndrome, and hyperaldosteronism including primary hyperaldosteronism (such as Conn's syndrome), secondary hyperaldosteronism, and familial hyperaldosteronism, and other diseases, disorders, and conditions.

[0310] The subject anti-ACTH antibodies and antibody fragments according to the invention can in particular be used for treating any subject wherein blocking, inhibiting or neutralizing the *in vivo* effect of ACTH or blocking or inhibiting the interaction of ACTH and MCRs is therapeutically desirable, wherein the subject anti-ACTH antibodies or antibody fragments may be used alone or in association with other active agents or drugs.

[0311] Said treatment may include administration of another agent. Exemplary agents may be agents used for the treatment of a condition associated with ACTH, such as ACTH-driven hypercortisolism, acute coronary syndrome, acute heart failure, anxiety disorders, atherosclerosis, atrial fibrillation, cachexia, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), cardiac conditions, cardiac fibrosis, cardiovascular disorders, chronic renal failure, chronic stress syndrome, cognitive dysfunction, Alzheimer's disease, congestive heart

failure, Conn's syndrome, coronary heart diseases, Cushing's Disease, Cushing's Syndrome, depression, diabetes, endothelial dysfunction, exercise intolerance, familial hyperaldosteronism, fibrosis, galactorrhea, heart failure, hyperaldosteronism, hypercortisolemia, hypertension, hypokalemia, impaired cardiac function, increased formation of collagen, inflammation, metabolic syndrome, muscle atrophy, conditions associated with muscle atrophy, myocardiac fibrosis, nephropathy, obesity, post-myocardial infarction, primary hyperaldosteronism, remodeling following hypertension, renal failure, restenosis, secondary hyperaldosteronism, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), or syndrome X, or for the treatment of a related condition such as hypercholesterolemia.

[0312] Additional exemplary agents that may be administered include (i) angiotensin II receptor antagonist or a pharmaceutically acceptable salt thereof, (ii) HMG-Co-A reductase inhibitor or a pharmaceutically acceptable salt thereof, (iii) angiotensin converting enzyme (ACE) Inhibitor or a pharmaceutically acceptable salt thereof, (iv) calcium channel blocker (CCB) or a pharmaceutically acceptable salt thereof, (v) dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor or a pharmaceutically acceptable salt thereof, (vi) endothelin antagonist or a pharmaceutically acceptable salt thereof, (vii) renin inhibitor or a pharmaceutically acceptable salt thereof, (viii) diuretic or a pharmaceutically acceptable salt thereof, (ix) an ApoA-l mimic; (x) an anti-diabetic agent; (xi) an obesity-reducing agent; (xii) an aldosterone receptor blocker; (xiii) an endothelin receptor blocker; (xiv) a CETP inhibitor; (xv) an inhibitor of Na-K-ATPase membrane pump; (xvi) a beta-adrenergic receptor blocker or an alpha-adrenergic receptor blocker; and (xvii) a neutral endopeptidase (NEP) inhibitor; or any combination thereof.

[0313] Further non-limiting examples of drugs that may be co-administered with the subject antibodies or antibody fragments or used in the same therapeutic regimen include by way of example statins, ACE inhibitors, Angiotensin II receptor blockers (ARBs), antiarrhythmics, antiplatelet drugs, aspirin, beta blockers, amiodarone, digoxin, aspirin, anti-clotting agents, digoxin, diuretics, heart failure drugs, vasodilators, blood thinners, other anti-cholesterol drugs such as cholestyramine (Questran), gemfibrozil (Lopid, Gemcor), Omacor, and pantethine, other anti-hypertensives, antidiabetogenic drugs such as alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 inhibitors, insulin therapies, meglitinides, sulfonylurea, and thiazolidinediones, and other drugs used to treat hypertension and conditions that are frequently associated with hypertension (such as hypercholesterolemia, diabetes, metabolic syndrome, obesity, etc.).

[0314] ACE inhibitors may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the moieties may be jointly or separately administered by the same or different means of administration include by way of example: Capoten (captopril), Vasotec (enalapril), Prinivil, Zestril (lisinopril), Lotensin (benazepril), Monopril (fosinopril), Altace (ramipril),

Accupril (quinapril), Aceon (perindopril), Mavik (trandolapril), and Univasc (moexipril) as well as any pharmaceutically acceptable salts thereof.

[0315] ARBs may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the moieties may be jointly or separately administered by the same or different means of administration include by way of example: Cozaar (losartan), Diovan (valsartan), Avapro (irbesartan), Atacand (candesartan), Micardis (telmisartan), eprosartan, olmesartan, saprisartan, tasosartan, E-4177, SC-52458, and ZD8731, as well as any pharmaceutically acceptable salts thereof.

[0316] Antiarrhythmics may be used in combination with the subject anti-ACTH antibodies and antibody fragments include by way of example: Tambocor (flecainide), Procanbid (procainamide), Cordarone (amiodarone), and Betapace (sotalol).

[0317] Anticlotting agents which may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the moieties may be jointly or separately administered by the same or different means of administration include: Tissue plasminogen activator (tPA), Tenecteplase, Alteplase, Urokinase, Reteplase, and Streptokinase.

[0318] Beta-blockers may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the agents may be jointly or separately administered by the same or different means of administration include by way of example: Sectral (acebutolol), Zebeta (bisoprolol), Brevibloc (esmolol), Inderal (propranolol), Tenormin (atenolol), Normodyne, Trandate (labetalol), Coreg (carvedilol), Lopressor, and Toprol-XL (metoprolol).

[0319] Calcium channel blockers which may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the agents may be jointly or separately administered by the same or different means of administration include by way of example: Norvasc (amlodipine), Plendil (felodipine), Cardizem, Cardizem CD, Cardizem SR, Dilacor XR, Diltia XT, Tiazac (diltiazem), Calan, Calan SR, Covera-HS, Isoptin, Isoptin SR, Verelan, Verelan PM (verapamil), Adalat, Adalat CC, Procardia, Procardia XL (nifedipine), Cardene, Cardene SR (nicardipine), Sular (nisoldipine), Vascor (bepridil), and Caduet which is a combination of a statin cholesterol drug and amlodipine.

[0320] Diuretics which may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the agents may be jointly or separately administered by the same or different means of administration include by way of example Lasix (furosemide), Bumex (bumetanide), Demadex (torsemide), Esidrix (hydrochlorothiazide), Zaroxolyn (metolazone), Aldactone (spironolactone), ethacrynic acid, ethynacrylic acid, mersalyl with theophylline, mercaptomerin sodium, merethoxylline procaine, amiloride, triamterene, chlorothalidone, chlorothiazide, quinethazone, hydroflumethiazide, methylchlorothiazide, and dichlorphenamide, including any pharmaceutically acceptable salts thereof.

[0321] Heart failure drugs which may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the agents may be jointly or separately administered by the same or different means of administration include by way of example Dobutrex (dobutamine), and Primacor (milrinone).

[0322] Vasodilators which may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the agents may be jointly or separately administered by the same or different means of administration include by way of example Dilatrate-SR, Iso-Bid, Isonate, Isordil (isosorbide dinitrate), Isotrate, Sorbitrate (isosorbide dinitrate), IMDUR (isosorbide mononitrate), and BiDil (hydralazine with isosorbide dinitrate.

[0323] Blood thinners which may be used in combination with the subject anti-ACTH antibodies and antibody fragments wherein the agents may be jointly or separately administered by the same or different means of administration include by way of example warfarin (Coumadin), Heparin, Lovenox, and Fragmin.

[0324] The subject anti-ACTH antibodies and antibody fragments according to the invention can further in particular be used for treating any subject wherein reducing cortisol and/or corticosterone levels is prophylactically or therapeutically desirable, wherein the subject anti-ACTH antibodies or antibody fragments may be used alone or in association with other active agents or drugs. These conditions include by way of example Cushing's Disease, Cushing's Syndrome, obesity, diabetes, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), depression, anxiety disorders, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), muscle atrophy, hypertension, hyperinsulinemia, cognitive dysfunction, Alzheimer's disease, galactorrhea, stress related conditions, impaired cardiac function, exercise intolerance, heart failure and other cardiac conditions, metabolic syndrome, hyperaldosteronism including primary hyperaldosteronism (such as Conn's syndrome) secondary hyperaldosteronism, and familial hyperaldosteronism, and other diseases, disorders, and conditions.

[0325] The subject anti-ACTH antibodies and antibody fragments according to the invention can also be used in any of the aforementioned therapeutic indications or conditions in combination with other drugs that are typically used to treat such disorders, wherein the antibody and other drug or agent may be co-administered or separately administered.

[0326] In particular, there are several pharmacological approaches to the treatment of Cushing's disease and/or Cushing's Syndrome. Drugs used to suppress cortisol secretion are mostly inhibitors of steroidogenesis, including, but not limited to, ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) and etomidate (Amidate®). Drugs that suppress adrenocorticotropic hormone (ACTH) secretion, e.g., cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), somatostatin analogs (e.g.,

pasireotide (Signifor®)), PPAR-gamma agonists (e.g., rosiglitazone (Avandia®)), vasopressin antagonists (i.e., Vaptans, including, but not limited to, conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), and satavaptan (SR121463, planned trade name Aquilda®)), may also be used. A third category of drugs is glucocorticoid receptor antagonists, e.g., mifepristone (Korlym®).

[0327] As noted above, the subject anti-ACTH antibodies may be used for the prevention or treatment of diseases and conditions associated with elevated aldosterone, and/or diseases and conditions treatable by decreasing aldosterone. Said diseases and conditions include hypertension, cardiovascular disorders, impaired cardiac function, exercise intolerance, heart failure (including congestive heart failure and acute heart failure), cardiac conditions, hypokalemia, atrial fibrillation, renal failure (e.g., chronic renal failure), restenosis, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, inflammation, increased formation of collagen, fibrosis such as cardiac or myocardiac fibrosis and remodeling following hypertension, endothelial dysfunction, cachexia, acute coronary syndrome, chronic stress syndrome, Cushing's disease, Cushing's Syndrome, metabolic syndrome, hypercortisolemia, and hyperaldosteronism (including primary hyperaldosteronism, secondary hyperaldosteronism, and familial hyperaldosteronism).

[0328] Additionally, there are several approaches to the management and/or treatment of sleep disorders, such as sleep apnea, insomnia or narcolepsy, ranging from lifestyle changes, such as losing weight or quitting smoking, to supplemental oxygen, medical devices, surgery and/or pharmaceuticals such as antidepressants and other drugs. Using supplemental oxygen while you sleep may treat sleep apnea. Various forms of oxygen are available as well as different devices to deliver oxygen to your lungs. Exemplary therapies include, but are not limited to, continuous positive airway pressure (CPAP); adjustable airway pressure devices (e.g., BPAP); expiratory positive airway pressure (EPAP); and oral appliances. CPAP therapy uses a machine to deliver air pressure, which is somewhat greater than that of the surrounding air, to keep your upper airway passages open, preventing apnea and snoring. Adjustable airway pressure devices provide an automatically adjusted air pressure to a subject while sleeping. For example, bilevel positive airway pressure (BPAP) therapy used a device that provides more pressure when you inhale and less when you exhale. EPAP is a small, single-use device that is placed over each nostril before going to sleep. The device is a valve that allows air to move freely in, but when you exhale, air must go through small holes in the valve which increases pressure in the airway and keeps it open. Also, adaptive servo-ventilation (ASV) is an airflow device that "learns" a person's normal breathing pattern and stores the information in a built-in computer so that after falling asleep, the machine uses pressure to normalize the breathing pattern and prevent pauses in your breathing. Another option is wearing an oral appliance designed to keep your throat open, e.g., by bringing your jaw forward. Additionally, surgical intervention (i.e., to enlarge the

airway through your nose or throat) is another approach to the treatment of sleep apnea. Exemplary surgical options include, but are not limited to, tissue removal (i.e., uvulopalatopharyngoplasty (UPPP) and/or removal of tonsils and adenoids); jaw repositioning (i.e., maxillomandibular advancement); implants (e.g., implanting plastic rods into the soft palate); creating a new air passageway (i.e., tracheostomy); nasal surgery to remove polyps or straighten a crooked partition between your nostrils (e.g., deviated nasal septum); and surgery to remove enlarged tonsils or adenoids. Additionally, treating medical problems associated with sleep apnea, e.g., heart or neuromuscular disorders, may improve and/or eliminate the symptoms of central sleep apnea. Finally, drugs used to treat sleep apnea include, but are not limited to, armodafinil (Nuvigil®) and modafinil (Provigil®).

[0329] Examples of drugs that may be co-administered with the subject anti-ACTH antibodies or antibody fragments or in the same therapeutic regimen include, by way of example, ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil (Provigil®), and other drugs used to treat conditions wherein the treated individual may have elevated ACTH levels. Further, examples of drugs that may be co-administered with the subject anti-ACTH antibodies or antibody fragments or in the same therapeutic regimen include without limitation thereto one or more of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-I mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate

(Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor (milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), or Zestril (lisinopril).

[0330] It should also be noted that the anti-ACTH antibodies or antibody fragments of the present invention may be used in conjunction with any of the described non-pharmaceutical based therapies for sleep apnea. Accordingly, in one embodiment, the anti-ACTH antibodies or antibody fragments are used in combination with one or more of lifestyle changes, supplemental oxygen, medical devices, and surgery to treat sleep apnea.

[0331] The invention further relates to compositions containing the subject anti-ACTH antibodies or antibody fragments, especially compositions are suitable for *in vivo* administration, e.g., subcutaneous, intravenous, intradermal, intranasal, intrathecal, vaginal, rectal, and other injectable administrable dosage forms.

[0332] More specifically, the invention provides compositions containing the subject anti-ACTH antibodies or antibody fragments, especially compositions which are suitable for *in vivo* administration, e.g., subcutaneous, intravenous, intradermal, intranasal, intrathecal, vaginal, rectal, oral and other injectable dosage forms which optionally may contain another active agent such as ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil

(Provigil®), and other drugs used to treat conditions wherein the treated individual may have elevated ACTH levels. Further examples of other active agent(s) that may optionally be contained in said dosage form include without limitation thereto one or more of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-I mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor (milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists,

Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), or Zestril (lisinopril).

[0333] The invention also provides novel dosage regimens using the subject anti-ACTH antibodies or antibody fragments, alone or in association with another active, especially subcutaneous, oral and intravenous dosing regimens.

[0334] Other uses for the antibodies or antibody fragments according to the invention include, for example, diagnosis of ACTH-associated diseases or conditions and screening assays to determine the presence or absence of ACTH. Some of the antibodies or antibody fragments according to the invention described herein are useful in treating consequences, symptoms, and/or the pathology associated with ACTH activity.

[0335] Exemplary anti-ACTH antibodies and antibody fragments according to the invention, and the specific CDRs thereof are identified in the following section. For the reader's convenience, each exemplified antibody or fragment, and sequences contained therein, are separately described under a Header that identifies the exemplified antibody by a specific nomenclature, i.e., Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[0336] Antibody Ab1

[0337] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSVKESGGRLVTPGTPLTLTCTVSGFSLSNYDMIWVRQAPGKGLESIGMIYDDGDTYYASWA
KGRFTISKTSTTVDLKIISPTTEDTATYFCVKGVSNHWGPGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK (SEQ ID NO: 1).

[0338] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0339] QSVKESGGRLVTPGTPLTLTCTVSGFSLSNYDMIWVRQAPGKGLESIGMIYDDGD
TYYASWAKGRFTISKTSTTVDLKIISPTTEDTATYFCVKGVSNHWGPGTLVTVSS (SEQ ID NO: 2).

[0340] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab1 and which contain a

constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 10).

[0341] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:
DVVMTQTPASVEAAVGGTVTIKCQASQSISSYLAWYQQKPGQPPKLLIYSASTLASGVPSRFK
GRGSGTEFTLTISDLECADAATYYCQSYDGSSGSSYGVGFGGGTEVVVKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 21).

[0342] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:
DVVMTQTPASVEAAVGGTVTIKCQASQSISSYLAWYQQKPGQPPKLLIYSASTLASGVPSRFK
GRGSGTEFTLTISDLECADAATYYCQSYDGSSGSSYGVGFGGGTEVVVKR (SEQ ID NO: 22).

[0343] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab1 which contain a constant light chain sequence comprising the sequence set forth below:
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD
STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 30).

[0344] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 6; and SEQ ID NO: 8 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1 or which contain the variable heavy chain sequence of SEQ ID NO: 2, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 24; SEQ ID NO: 26; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 21 or which contain the variable light chain sequence of SEQ ID NO: 22, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of

one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0345] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 3; SEQ ID NO: 5; SEQ ID NO: 7; and SEQ ID NO: 9 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 1 or the variable heavy chain sequence of SEQ ID NO: 2, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 25; SEQ ID NO: 27; and SEQ ID NO: 29 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 21 or the variable light chain sequence of SEQ ID NO: 22, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0346] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0347] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 1 or SEQ ID NO: 2 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 21 or SEQ ID NO: 22 or polypeptides that are at least 90% or 95% identical thereto.

[0348] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 4; SEQ ID NO: 6; and SEQ ID NO: 8 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1 or the variable heavy chain sequence of SEQ ID NO: 2 or sequences that are at least 90% or 95% identical thereto.

[0349] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 24; SEQ ID NO: 26; and SEQ ID NO: 28 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 21 or the variable light chain sequence of SEQ ID NO: 22 or sequences that are at least 90% or 95% identical thereto.

[0350] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 3; SEQ ID NO: 5; SEQ ID NO: 7; and SEQ ID NO: 9 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 1 or the variable heavy chain sequence of SEQ ID NO: 2 or sequences that are at least 90% or 95% identical thereto.

[0351] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 23; SEQ ID NO: 25; SEQ ID NO: 27; and SEQ ID NO: 29 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 21 or the variable light chain sequence of SEQ ID NO: 22 or sequences that are at least 90% or 95% identical thereto.

[0352] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 2; the variable light chain region of SEQ ID NO: 22; the complementarity-determining regions (SEQ ID NO: 4; SEQ ID NO: 6; and SEQ ID NO: 8) of the variable heavy chain region of SEQ ID NO: 2; and the complementarity-determining regions (SEQ ID NO: 24; SEQ ID NO: 26; and SEQ ID NO: 28) of the variable light chain region of SEQ ID NO: 22 or sequences that are at least 90% or 95% identical thereto.

[0353] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 2; the variable light chain region of SEQ ID NO: 22; the framework regions (SEQ ID NO: 3; SEQ ID NO: 5; SEQ ID NO: 7; and SEQ ID NO: 9) of the variable heavy chain region of SEQ ID NO: 2; and the framework regions (SEQ ID NO: 23; SEQ ID NO: 25; SEQ ID NO: 27; and SEQ ID NO: 29) of the variable light chain region of SEQ ID NO: 22.

[0354] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab1, comprising, or alternatively consisting of, SEQ ID NO: 1 and SEQ ID NO: 21 or SEQ ID NO: 2 and SEQ ID NO: 22, or an antibody or antibody fragment comprising the CDRs of Ab1 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab1 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab1 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab1.

[0355] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab1, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 2 and the variable light chain sequence of SEQ ID NO: 22 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 2 and/or SEQ ID NO: 22 which retain the binding specificity for ACTH.

[0356] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab1. In another embodiment of the invention, anti-ACTH antibodies such as Ab1 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0357] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab1 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0358] Antibody Ab2

[0359] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLTCTVSGFSLSKYDMIWVRQAPGKGLESIGIIYDDGDTYYASWAK
GRFTISQTSTTVDLKIISPTTEDTATYFCVKGVSNIWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
GK (SEQ ID NO: 41).

[0360] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0361] QSVEESGGRLVTPGTPLTLTCTVSGFSLSKYDMIWVRQAPGKGLESIGIIYDDGDT
YYASWAKGRFTISQTSTTVDLKIISPTTEDTATYFCVKGVSNIWGQGTLVTVSS (SEQ ID NO: 42).

[0362] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab2 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 50).

[0363] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:
DVVMTQTPASVEAAVGGTVTIKCQASQSISNYLAWYQQKTGQPPKLLIYSASTLASGVPSRF
KGSGSGTEFTLTISDLECADAATYYCQSYEGSSSSSYGVGFGGGTEVVVKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 61).

[0364] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:
DVVMTQTPASVEAAVGGTVTIKCQASQSISNYLAWYQQKTGQPPKLLIYSASTLASGVPSRF
KGSGSGTEFTLTISDLECADAATYYCQSYEGSSSSSYGVGFGGGTEVVVKR (SEQ ID NO: 62).

[0365] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab2 which contain a constant light chain sequence comprising the sequence set forth below:
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD
STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 70).

[0366] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 44; SEQ ID NO: 46; and SEQ ID NO: 48 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 41 or which contain the variable heavy chain sequence of SEQ ID NO: 42, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 64; SEQ ID NO: 66; and SEQ ID NO: 68 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 61 or which contain the variable light chain sequence of SEQ ID NO: 62, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%,

90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0367] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 43; SEQ ID NO: 45; SEQ ID NO: 47; and SEQ ID NO: 49 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 41 or the variable heavy chain sequence of SEQ ID NO: 42, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 63; SEQ ID NO: 65; SEQ ID NO: 67; and SEQ ID NO: 69 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 61 or the variable light chain sequence of SEQ ID NO: 62, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0368] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0369] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 41 or SEQ ID NO: 42 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 61 or SEQ ID NO: 62 or polypeptides that are at least 90% or 95% identical thereto.

[0370] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 44; SEQ ID NO: 46; and SEQ ID NO: 48 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 41 or the variable heavy chain sequence of SEQ ID NO: 42 or sequences that are at least 90% or 95% identical thereto.

[0371] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 64; SEQ ID NO: 66; and SEQ ID NO: 68 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain

sequence of SEQ ID NO: 61 or the variable light chain sequence of SEQ ID NO: 62 or sequences that are at least 90% or 95% identical thereto.

[0372] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 43; SEQ ID NO: 45; SEQ ID NO: 47; and SEQ ID NO: 49 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 41 or the variable heavy chain sequence of SEQ ID NO: 42 or sequences that are at least 90% or 95% identical thereto.

[0373] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 63; SEQ ID NO: 65; SEQ ID NO: 67; and SEQ ID NO: 69 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 61 or the variable light chain sequence of SEQ ID NO: 62 or sequences that are at least 90% or 95% identical thereto.

[0374] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 42; the variable light chain region of SEQ ID NO: 62; the complementarity-determining regions (SEQ ID NO: 44; SEQ ID NO: 46; and SEQ ID NO: 48) of the variable heavy chain region of SEQ ID NO: 42; and the complementarity-determining regions (SEQ ID NO: 64; SEQ ID NO: 66; and SEQ ID NO: 68) of the variable light chain region of SEQ ID NO: 62 or sequences that are at least 90% or 95% identical thereto.

[0375] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 42; the variable light chain region of SEQ ID NO: 62; the framework regions (SEQ ID NO: 43; SEQ ID NO: 45; SEQ ID NO: 47; and SEQ ID NO: 49) of the variable heavy chain region of SEQ ID NO: 42; and the framework regions (SEQ ID NO: 63; SEQ ID NO: 65; SEQ ID NO: 67; and SEQ ID NO: 69) of the variable light chain region of SEQ ID NO: 62.

[0376] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab2, comprising, or alternatively consisting of, SEQ ID NO: 41 and SEQ ID NO: 61 or SEQ ID NO: 42 and SEQ ID NO: 62, or an antibody or antibody fragment comprising the CDRs of Ab2 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab2 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%,

98% or 99% identical to that of Ab2 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab2.

[0377] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab2, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 42 and the variable light chain sequence of SEQ ID NO: 62 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 42 and/or SEQ ID NO: 62 which retain the binding specificity for ACTH.

[0378] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab2. In another embodiment of the invention, anti-ACTH antibodies such as Ab2 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0379] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab2 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0380] Antibody Ab3

[0381] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSLEESGGRLVTPGTPLTLTCTVSGSSLSNFDMIWVRQAPGKGLESIGIIYDFGSTYYASWAK
GRFTISRTSSTTVDLKIISPTIEDTATYFCVKGVSNIWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
GK (SEQ ID NO: 81).

[0382] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0383] QSLEESGGRLVTPGTPLTLTCTVSGSSLSNFDMIWVRQAPGKGLESIGIIYDFGSTY YASWAKGRFTISRTSSTTVDLKIISPTIEDTATYFCVKGVSNIWGQGTLVTVSS (SEQ ID NO: 82).

[0384] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab3 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 90).

[0385] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:
DVVMTQTPASVEAAVGGTVTIKCQASEDISSNLAWYQQKLGQPPKLLIYSASTLASGVPSRF KGSGSGTEFTLAISDLECADAATYYCQSYDGSSSSSYGIGFGGGTEVVVKRTVAAPSVFIFPPS DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 101).

[0386] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:
DVVMTQTPASVEAAVGGTVTIKCQASEDISSNLAWYQQKLGQPPKLLIYSASTLASGVPSRF KGSGSGTEFTLAISDLECADAATYYCQSYDGSSSSSYGIGFGGGTEVVVKR (SEQ ID NO: 102).

[0387] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab3 which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 110).

[0388] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 84; SEQ ID NO: 86; and SEQ ID NO: 88 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 81 or which contain the variable heavy chain sequence of SEQ ID NO: 82, and/or which further contain one, two,

or three of the polypeptide sequences of SEQ ID NO: 104; SEQ ID NO: 106; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 101 or which contain the variable light chain sequence of SEQ ID NO: 102, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0389] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 83; SEQ ID NO: 85; SEQ ID NO: 87; and SEQ ID NO: 89 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 81 or the variable heavy chain sequence of SEQ ID NO: 82, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 105; SEQ ID NO: 107; and SEQ ID NO: 109 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 101 or the variable light chain sequence of SEQ ID NO: 102, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0390] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0391] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 81 or SEQ ID NO: 82 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 101 or SEQ ID NO: 102 or polypeptides that are at least 90% or 95% identical thereto.

[0392] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 84; SEQ ID NO: 86; and SEQ ID NO: 88 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 81 or the variable heavy chain sequence of SEQ ID NO: 82 or sequences that are at least 90% or 95% identical thereto.

[0393] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 104; SEQ ID NO: 106; and SEQ ID NO: 108 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 101 or the variable light chain sequence of SEQ ID NO: 102 or sequences that are at least 90% or 95% identical thereto.

[0394] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 83; SEQ ID NO: 85; SEQ ID NO: 87; and SEQ ID NO: 89 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 81 or the variable heavy chain sequence of SEQ ID NO: 82 or sequences that are at least 90% or 95% identical thereto.

[0395] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 103; SEQ ID NO: 105; SEQ ID NO: 107; and SEQ ID NO: 109 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 101 or the variable light chain sequence of SEQ ID NO: 102 or sequences that are at least 90% or 95% identical thereto.

[0396] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 82; the variable light chain region of SEQ ID NO: 102; the complementarity-determining regions (SEQ ID NO: 84; SEQ ID NO: 86; and SEQ ID NO: 88) of the variable heavy chain region of SEQ ID NO: 82; and the complementarity-determining regions (SEQ ID NO: 104; SEQ ID NO: 106; and SEQ ID NO: 108) of the variable light chain region of SEQ ID NO: 102 or sequences that are at least 90% or 95% identical thereto.

[0397] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 82; the variable light chain region of SEQ ID NO: 102; the framework regions (SEQ ID NO: 83; SEQ ID NO: 85; SEQ ID NO: 87; and SEQ ID NO: 89) of the variable heavy chain region of SEQ ID NO: 82; and the framework regions (SEQ ID NO: 103; SEQ ID NO: 105; SEQ ID NO: 107; and SEQ ID NO: 109) of the variable light chain region of SEQ ID NO: 102.

[0398] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab3, comprising, or alternatively consisting of, SEQ ID NO: 81 and SEQ ID NO: 101 or SEQ ID NO: 82 and SEQ ID NO: 102, or an antibody or antibody fragment comprising the CDRs of Ab3 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab3 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab3 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab3.

[0399] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab3, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 82 and the variable light chain sequence of SEQ ID NO: 102 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 82 and/or SEQ ID NO: 102 which retain the binding specificity for ACTH.

[0400] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab3. In another embodiment of the invention, anti-ACTH antibodies such as Ab3 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0401] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab3 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0402] Antibody Ab4

[0403] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLTYTVSGFSLSKHDMIWVRQAPGKGLESIGIIYDDGDTYYANWA
KGRFTISKTSTTVDLKIISPTTEDTATYFCVKGVSNIWGPGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES

NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK (SEQ ID NO: 121).

[0404] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0405] QSVEESGGRLVTPGTPLTLTYTVSGFSLSKHDMIWVRQAPGKGLESIGIIYDDGDT YYANWAKGRFTISKTSTTVDLKIISPTTEDTATYFCVKGVSNIWGPGTLVTVSS (SEQ ID NO: 122).

[0406] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab4 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 130).

[0407] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DVVMTQTPASVEAAVGGTVTIKCRASQSISVYLAWYQQKAGQPPKLLIYQASKLASGVPSRF KGSGSGTEFTLTISDLECADAATYYCQSYDGSSSSSYGVGFGGGTEVVVKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 141).

[0408] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DVVMTQTPASVEAAVGGTVTIKCRASQSISVYLAWYQQKAGQPPKLLIYQASKLASGVPSRF KGSGSGTEFTLTISDLECADAATYYCQSYDGSSSSSYGVGFGGGTEVVVKR (SEQ ID NO: 142).

[0409] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab4 which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 150).

[0410] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 126; and SEQ ID NO: 128 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 121 or which contain the variable heavy chain sequence of SEQ ID NO: 122, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 144; SEQ ID NO: 146; and SEQ ID NO: 148 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 141 or which contain the variable light chain sequence of SEQ ID NO: 142, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0411] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 123; SEQ ID NO: 125; SEQ ID NO: 127; and SEQ ID NO: 129 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 121 or the variable heavy chain sequence of SEQ ID NO: 122, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 145; SEQ ID NO: 147; and SEQ ID NO: 149 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 141 or the variable light chain sequence of SEQ ID NO: 142, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0412] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0413] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 121 or SEQ ID NO: 122 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 141 or SEQ ID NO: 142 or polypeptides that are at least 90% or 95% identical thereto.

[0414] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the

polypeptide sequences of SEQ ID NO: 124; SEQ ID NO: 126; and SEQ ID NO: 128 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 121 or the variable heavy chain sequence of SEQ ID NO: 122 or sequences that are at least 90% or 95% identical thereto.

[0415] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 144; SEQ ID NO: 146; and SEQ ID NO: 148 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 141 or the variable light chain sequence of SEQ ID NO: 142 or sequences that are at least 90% or 95% identical thereto.

[0416] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 123; SEQ ID NO: 125; SEQ ID NO: 127; and SEQ ID NO: 129 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 121 or the variable heavy chain sequence of SEQ ID NO: 122 or sequences that are at least 90% or 95% identical thereto.

[0417] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 143; SEQ ID NO: 145; SEQ ID NO: 147; and SEQ ID NO: 149 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 141 or the variable light chain sequence of SEQ ID NO: 142 or sequences that are at least 90% or 95% identical thereto.

[0418] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 122; the variable light chain region of SEQ ID NO: 142; the complementarity-determining regions (SEQ ID NO: 124; SEQ ID NO: 126; and SEQ ID NO: 128) of the variable heavy chain region of SEQ ID NO: 122; and the complementarity-determining regions (SEQ ID NO: 144; SEQ ID NO: 146; and SEQ ID NO: 148) of the variable light chain region of SEQ ID NO: 142 or sequences that are at least 90% or 95% identical thereto.

[0419] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 122; the variable light chain region of SEQ ID NO: 142; the framework regions (SEQ ID NO:

123; SEQ ID NO: 125; SEQ ID NO: 127; and SEQ ID NO: 129) of the variable heavy chain region of SEQ ID NO: 122; and the framework regions (SEQ ID NO: 143; SEQ ID NO: 145; SEQ ID NO: 147; and SEQ ID NO: 149) of the variable light chain region of SEQ ID NO: 142.

[0420] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab4, comprising, or alternatively consisting of, SEQ ID NO: 121 and SEQ ID NO: 141 or SEQ ID NO: 122 and SEQ ID NO: 142, or an antibody or antibody fragment comprising the CDRs of Ab4 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab4 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab4 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab4.

[0421] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab4, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 122 and the variable light chain sequence of SEQ ID NO: 142 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 122 and/or SEQ ID NO: 142 which retain the binding specificity for ACTH.

[0422] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab4. In another embodiment of the invention, anti-ACTH antibodies such as Ab4 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0423] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab4 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0424] Antibody Ab5

[0425] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGEGLEWIGIISDSGSTYYASWAK
GRFTISKTSTTVDLKITSPTTEDTATYFCAREPEYGYDDYGDWVSDLWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP

KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK (SEQ ID NO: 161).

[0426] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0427] QSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGEGLEWIGIISDSGSTY YASWAKGRFTISKTSTTVDLKITSPTTEDTATYFCAREPEYGYDDYGDWVSDLWGQGTLVT VSS (SEQ ID NO: 162).

[0428] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab5 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 170).

[0429] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

ADIVMTQTPASVSEPVGGTVTIKCQASQSISSYLSWYQQKPGQPPKLLIYRASTLASGVPSRFK GSGSGTQFTLTISDLECADAATYYCQSYYYSSSITYRNAFGGGTEVVVKRTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 181).

[0430] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

ADIVMTQTPASVSEPVGGTVTIKCQASQSISSYLSWYQQKPGQPPKLLIYRASTLASGVPSRFK GSGSGTQFTLTISDLECADAATYYCQSYYYSSSITYRNAFGGGTEVVVKR (SEQ ID NO: 182).

[0431] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab5 which contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 190).

[0432] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 164; SEQ ID NO: 166; and SEQ ID NO: 168 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 161 or which contain the variable heavy chain sequence of SEQ ID NO: 162, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 184; SEQ ID NO: 186; and SEQ ID NO: 188 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 181 or which contain the variable light chain sequence of SEQ ID NO: 182, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0433] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 163; SEQ ID NO: 165; SEQ ID NO: 167; and SEQ ID NO: 169 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 161 or the variable heavy chain sequence of SEQ ID NO: 162, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 183; SEQ ID NO: 185; SEQ ID NO: 187; and SEQ ID NO: 189 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 181 or the variable light chain sequence of SEQ ID NO: 182, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0434] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0435] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 161 or SEQ ID NO: 162 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 181 or SEQ ID NO: 182 or polypeptides that are at least 90% or 95% identical thereto.

[0436] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 164; SEQ ID NO: 166; and SEQ ID NO: 168 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 161 or the variable heavy chain sequence of SEQ ID NO: 162 or sequences that are at least 90% or 95% identical thereto.

[0437] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 184; SEQ ID NO: 186; and SEQ ID NO: 188 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 181 or the variable light chain sequence of SEQ ID NO: 182 or sequences that are at least 90% or 95% identical thereto.

[0438] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 163; SEQ ID NO: 165; SEQ ID NO: 167; and SEQ ID NO: 169 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 161 or the variable heavy chain sequence of SEQ ID NO: 162 or sequences that are at least 90% or 95% identical thereto.

[0439] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 183; SEQ ID NO: 185; SEQ ID NO: 187; and SEQ ID NO: 189 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 181 or the variable light chain sequence of SEQ ID NO: 182 or sequences that are at least 90% or 95% identical thereto.

[0440] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 162; the variable light chain region of SEQ ID NO: 182; the complementarity-determining regions (SEQ ID NO: 164; SEQ ID NO: 166; and SEQ ID NO: 168) of the variable heavy chain region of SEQ ID NO: 162; and the complementarity-determining regions (SEQ ID NO: 184; SEQ ID NO: 186; and SEQ ID NO: 188) of the variable light chain region of SEQ ID NO: 182 or sequences that are at least 90% or 95% identical thereto.

[0441] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or

more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 162; the variable light chain region of SEQ ID NO: 182; the framework regions (SEQ ID NO: 163; SEQ ID NO: 165; SEQ ID NO: 167; and SEQ ID NO: 169) of the variable heavy chain region of SEQ ID NO: 162; and the framework regions (SEQ ID NO: 183; SEQ ID NO: 185; SEQ ID NO: 187; and SEQ ID NO: 189) of the variable light chain region of SEQ ID NO: 182.

[0442] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab5, comprising, or alternatively consisting of, SEQ ID NO: 161 and SEQ ID NO: 181 or SEQ ID NO: 162 and SEQ ID NO: 182, or an antibody or antibody fragment comprising the CDRs of Ab5 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab5 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab5 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab5.

[0443] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab5, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 162 and the variable light chain sequence of SEQ ID NO: 182 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 162 and/or SEQ ID NO: 182 which retain the binding specificity for ACTH.

[0444] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab5. In another embodiment of the invention, anti-ACTH antibodies such as Ab5 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0445] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab5 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0446] Antibody Ab6

[0447] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLTCTVSGFSLTDYAMSWVRQAPGEGLEWIGIISDSGSTYYASWA
KGRFTFSKTSTTVDLRITSPTTEDTATYFCAREPEYGYDEYGDWVSDLWGPGTLVTVSSAST

KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK (SEQ ID NO: 201).

[0448] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0449] QSVEESGGRLVTPGTPLTLTCTVSGFSLTDYAMSWVRQAPGEGLEWIGIISDSGST YYASWAKGRFTFSKTSTTVDLRITSPTTEDTATYFCAREPEYGYDEYGDWVSDLWGPGTLVT VSS (SEQ ID NO: 202).

[0450] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab6 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 210).

[0451] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

ADIVMTQTPASVEAAVGGAVTIKCQATQSIGNNLAWYQQKPGQPPKLLIYRASTLASGVPSR FKGSGSGTEFTLTISDLECADAATYYCQSYYYSSSITYHNAFGGGTEVVVKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 221).

[0452] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

ADIVMTQTPASVEAAVGGAVTIKCQATQSIGNNLAWYQQKPGQPPKLLIYRASTLASGVPSR FKGSGSGTEFTLTISDLECADAATYYCQSYYYSSSITYHNAFGGGTEVVVKR (SEQ ID NO: 222).

[0453] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab6 which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 230).

[0454] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 201 or which contain the variable heavy chain sequence of SEQ ID NO: 202, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 221 or which contain the variable light chain sequence of SEQ ID NO: 222, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0455] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 203; SEQ ID NO: 205; SEQ ID NO: 207; and SEQ ID NO: 209 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 201 or the variable heavy chain sequence of SEQ ID NO: 202, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 225; SEQ ID NO: 227; and SEQ ID NO: 229 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 221 or the variable light chain sequence of SEQ ID NO: 222, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0456] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0457] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 201 or SEQ ID NO: 202 or polypeptides that are at least 90% or 95% identical thereto. In another

embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 221 or SEQ ID NO: 222 or polypeptides that are at least 90% or 95% identical thereto.

[0458] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 201 or the variable heavy chain sequence of SEQ ID NO: 202 or sequences that are at least 90% or 95% identical thereto.

[0459] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 221 or the variable light chain sequence of SEQ ID NO: 222 or sequences that are at least 90% or 95% identical thereto.

[0460] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 203; SEQ ID NO: 205; SEQ ID NO: 207; and SEQ ID NO: 209 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 201 or the variable heavy chain sequence of SEQ ID NO: 202 or sequences that are at least 90% or 95% identical thereto.

[0461] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 223; SEQ ID NO: 225; SEQ ID NO: 227; and SEQ ID NO: 229 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 221 or the variable light chain sequence of SEQ ID NO: 222 or sequences that are at least 90% or 95% identical thereto.

[0462] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 202; the variable light chain region of SEQ ID NO: 222; the complementarity-determining regions (SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208) of the variable heavy chain region of SEQ ID NO: 202; and the complementarity-determining regions (SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228) of the variable light chain region of SEQ ID NO: 222 or sequences that are at least 90% or 95% identical thereto.

[0463] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 202; the variable light chain region of SEQ ID NO: 222; the framework regions (SEQ ID NO: 203; SEQ ID NO: 205; SEQ ID NO: 207; and SEQ ID NO: 209) of the variable heavy chain region of SEQ ID NO: 202; and the framework regions (SEQ ID NO: 223; SEQ ID NO: 225; SEQ ID NO: 227; and SEQ ID NO: 229) of the variable light chain region of SEQ ID NO: 222.

[0464] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab6, comprising, or alternatively consisting of, SEQ ID NO: 201 and SEQ ID NO: 221 or SEQ ID NO: 202 and SEQ ID NO: 222, or an antibody or antibody fragment comprising the CDRs of Ab6 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab6 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab6 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab6.

[0465] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab6, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 202 and the variable light chain sequence of SEQ ID NO: 222 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 202 and/or SEQ ID NO: 222 which retain the binding specificity for ACTH.

[0466] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6. In another embodiment of the invention, anti-ACTH antibodies such as Ab6 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0467] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab6 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0468] Antibody Ab7

[0469] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth

below:

QSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGEGLEWIGIISDSGSTYYASWAK
GRFTISKTSTTVDLRITSPTTEDTATYFCAREPEYGYDDYGDWVSDLWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK (SEQ ID NO: 241).

[0470] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0471] QSVEESGGRLVTPGTPLTLTCTVSGFSLSSYAMSWVRQAPGEGLEWIGIISDSGSTY
YASWAKGRFTISKTSTTVDLRITSPTTEDTATYFCAREPEYGYDDYGDWVSDLWGQGTLVT
VSS (SEQ ID NO: 242).

[0472] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab7 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 250).

[0473] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

ADIVMTQTPASVEAAVGGTVTIKCQASQSISDYLSWYQQKPGQPPKLLIYRASTLASGVPSRF
KGSGSGTQFTLTISDLECADAATYYCQSYYYSSSITYRNAFGGGTEVVVKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 261).

[0474] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

ADIVMTQTPASVEAAVGGTVTIKCQASQSISDYLSWYQQKPGQPPKLLIYRASTLASGVPSRF

KGSGSGTQFTLTISDLECADAATYYCQSYYYSSSITYRNAFGGGTEVVVKR (SEQ ID NO: 262).

[0475] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab7 which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 270).

[0476] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 244; SEQ ID NO: 246; and SEQ ID NO: 248 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 241 or which contain the variable heavy chain sequence of SEQ ID NO: 242, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 264; SEQ ID NO: 266; and SEQ ID NO: 268 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 261 or which contain the variable light chain sequence of SEQ ID NO: 262, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0477] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 243; SEQ ID NO: 245; SEQ ID NO: 247; and SEQ ID NO: 249 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 241 or the variable heavy chain sequence of SEQ ID NO: 242, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 263; SEQ ID NO: 265; SEQ ID NO: 267; and SEQ ID NO: 269 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 261 or the variable light chain sequence of SEQ ID NO: 262, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0478] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0479] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 241 or SEQ ID NO: 242 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 261 or SEQ ID NO: 262 or polypeptides that are at least 90% or 95% identical thereto.

[0480] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 244; SEQ ID NO: 246; and SEQ ID NO: 248 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 241 or the variable heavy chain sequence of SEQ ID NO: 242 or sequences that are at least 90% or 95% identical thereto.

[0481] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 264; SEQ ID NO: 266; and SEQ ID NO: 268 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 261 or the variable light chain sequence of SEQ ID NO: 262 or sequences that are at least 90% or 95% identical thereto.

[0482] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 243; SEQ ID NO: 245; SEQ ID NO: 247; and SEQ ID NO: 249 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 241 or the variable heavy chain sequence of SEQ ID NO: 242 or sequences that are at least 90% or 95% identical thereto.

[0483] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 263; SEQ ID NO: 265; SEQ ID NO: 267; and SEQ ID NO: 269 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 261 or the variable light chain sequence of SEQ ID NO: 262 or sequences that are at least 90% or 95% identical thereto.

[0484] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 242; the variable light chain region of SEQ ID NO: 262; the complementarity-determining regions (SEQ ID NO: 244; SEQ ID NO: 246; and SEQ ID NO: 248) of the variable

heavy chain region of SEQ ID NO: 242; and the complementarity-determining regions (SEQ ID NO: 264; SEQ ID NO: 266; and SEQ ID NO: 268) of the variable light chain region of SEQ ID NO: 262 or sequences that are at least 90% or 95% identical thereto.

[0485] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 242; the variable light chain region of SEQ ID NO: 262; the framework regions (SEQ ID NO: 243; SEQ ID NO: 245; SEQ ID NO: 247; and SEQ ID NO: 249) of the variable heavy chain region of SEQ ID NO: 242; and the framework regions (SEQ ID NO: 263; SEQ ID NO: 265; SEQ ID NO: 267; and SEQ ID NO: 269) of the variable light chain region of SEQ ID NO: 262.

[0486] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab7, comprising, or alternatively consisting of, SEQ ID NO: 241 and SEQ ID NO: 261 or SEQ ID NO: 242 and SEQ ID NO: 262, or an antibody or antibody fragment comprising the CDRs of Ab7 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab7 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab7 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab7.

[0487] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab7, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 242 and the variable light chain sequence of SEQ ID NO: 262 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 242 and/or SEQ ID NO: 262 which retain the binding specificity for ACTH.

[0488] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab7. In another embodiment of the invention, anti-ACTH antibodies such as Ab7 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0489] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab7 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0490] Antibody Ab9

[0491] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLTCTVSGFSLNSYAMSWVRQAPGEGLEWIGIISDSGRTYYASWA
KGRFTISKTSTTVDLKITSPTTEDTATYFCAREPEYGYDDYGDWVSDLWGPGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTV
LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK (SEQ ID NO: 281).

[0492] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0493] QSVEESGGRLVTPGTPLTLTCTVSGFSLNSYAMSWVRQAPGEGLEWIGIISDSGRT
YYASWAKGRFTISKTSTTVDLKITSPTTEDTATYFCAREPEYGYDDYGDWVSDLWGPGTLVT
VSS (SEQ ID NO: 282).

[0494] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab9 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 290).

[0495] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

ADVVMTQTPASVEAAVGGTVTIKCQASQSISSYLSWYQQKPGQPPKLLIYRASTLASGVPSRF
KGSGSGTQFTLTISDLECADAATYYCQSYYYSSSITYRNAFGGGTEVVVKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 301).

[0496] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below: ADVVMTQTPASVEAAVGGTVTIKCQASQSISSYLSWYQQKPGQPPKLLIYRASTLASGVPSRF KGSGSGTQFTLTISDLECADAATYYCQSYYYSSSITYRNAFGGGTEVVVKR (SEQ ID NO: 302).

[0497] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab9 which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 310).

[0498] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 286; and SEQ ID NO: 288 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 281 or which contain the variable heavy chain sequence of SEQ ID NO: 282, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 304; SEQ ID NO: 306; and SEQ ID NO: 308 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 301 or which contain the variable light chain sequence of SEQ ID NO: 302, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0499] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 283; SEQ ID NO: 285; SEQ ID NO: 287; and SEQ ID NO: 289 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 281 or the variable heavy chain sequence of SEQ ID NO: 282, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 305; SEQ ID NO: 307; and SEQ ID NO: 309 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 301 or the variable light chain sequence of SEQ ID NO: 302, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0500] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of

the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0501] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 281 or SEQ ID NO: 282 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 301 or SEQ ID NO: 302 or polypeptides that are at least 90% or 95% identical thereto.

[0502] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 284; SEQ ID NO: 286; and SEQ ID NO: 288 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 281 or the variable heavy chain sequence of SEQ ID NO: 282 or sequences that are at least 90% or 95% identical thereto.

[0503] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 304; SEQ ID NO: 306; and SEQ ID NO: 308 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 301 or the variable light chain sequence of SEQ ID NO: 302 or sequences that are at least 90% or 95% identical thereto.

[0504] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 283; SEQ ID NO: 285; SEQ ID NO: 287; and SEQ ID NO: 289 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 281 or the variable heavy chain sequence of SEQ ID NO: 282 or sequences that are at least 90% or 95% identical thereto.

[0505] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 303; SEQ ID NO: 305; SEQ ID NO: 307; and SEQ ID NO: 309 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 301 or the variable light chain sequence of SEQ ID NO: 302 or sequences that are at least 90% or 95% identical thereto.

[0506] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one,

two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 282; the variable light chain region of SEQ ID NO: 302; the complementarity-determining regions (SEQ ID NO: 284; SEQ ID NO: 286; and SEQ ID NO: 288) of the variable heavy chain region of SEQ ID NO: 282; and the complementarity-determining regions (SEQ ID NO: 304; SEQ ID NO: 306; and SEQ ID NO: 308) of the variable light chain region of SEQ ID NO: 302 or sequences that are at least 90% or 95% identical thereto.

[0507] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 282; the variable light chain region of SEQ ID NO: 302; the framework regions (SEQ ID NO: 283; SEQ ID NO: 285; SEQ ID NO: 287; and SEQ ID NO: 289) of the variable heavy chain region of SEQ ID NO: 282; and the framework regions (SEQ ID NO: 303; SEQ ID NO: 305; SEQ ID NO: 307; and SEQ ID NO: 309) of the variable light chain region of SEQ ID NO: 302.

[0508] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab9, comprising, or alternatively consisting of, SEQ ID NO: 281 and SEQ ID NO: 301 or SEQ ID NO: 282 and SEQ ID NO: 302, or an antibody or antibody fragment comprising the CDRs of Ab9 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab9 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab9 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab9.

[0509] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab9, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 282 and the variable light chain sequence of SEQ ID NO: 302 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 282 and/or SEQ ID NO: 302 which retain the binding specificity for ACTH.

[0510] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab9. In another embodiment of the invention, anti-ACTH antibodies such as Ab9 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0511] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of

Ab9 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0512] Antibody Ab10

[0513] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLTCTVSGFSLSSADMIWVRQAPGKGLESIGMIYDDGDTYYATWA
KGRFTISKTSTTVDLKIISPTTEDTATYFCVKGVSSVWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK (SEQ ID NO: 321).

[0514] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0515] QSVEESGGRLVTPGTPLTLTCTVSGFSLSSADMIWVRQAPGKGLESIGMIYDDGDT
YYATWAKGRFTISKTSTTVDLKIISPTTEDTATYFCVKGVSSVWGQGTLVTVSS (SEQ ID NO:
322).

[0516] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab10 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 330).

[0517] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DVVMTQTPASVEAAVGGTVTINCQASENIYRSLAWYQQKPGQPPKLLIYSASTLASGVPSRF
KGSGSGTEFTLTISDLECADAATYYCQSYDGSSSSSYGVGFGGGTEVVVKRTVAAPSVFIFPP

SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 341).

[0518] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:
DVVMTQTPASVEAAVGGTVTINCQASENIYRSLAWYQQKPGQPPKLLIYSASTLASGVPSRF KGSGSGTEFTLTISDLECADAATYYCQSYDGSSSSSYGVGFGGGTEVVVKR (SEQ ID NO: 342).

[0519] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab10 which contain a constant light chain sequence comprising the sequence set forth below:
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 350).

[0520] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 324; SEQ ID NO: 326; and SEQ ID NO: 328 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 321 or which contain the variable heavy chain sequence of SEQ ID NO: 322, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 344; SEQ ID NO: 346; and SEQ ID NO: 348 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 341 or which contain the variable light chain sequence of SEQ ID NO: 342, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0521] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 323; SEQ ID NO: 325; SEQ ID NO: 327; and SEQ ID NO: 329 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 321 or the variable heavy chain sequence of SEQ ID NO: 322, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 343; SEQ ID NO: 345; SEQ ID NO: 347; and SEQ ID NO: 349 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 341 or the variable light chain sequence of SEQ ID NO: 342, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0522] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0523] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 321 or SEQ ID NO: 322 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 341 or SEQ ID NO: 342 or polypeptides that are at least 90% or 95% identical thereto.

[0524] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 324; SEQ ID NO: 326; and SEQ ID NO: 328 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 321 or the variable heavy chain sequence of SEQ ID NO: 322 or sequences that are at least 90% or 95% identical thereto.

[0525] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 344; SEQ ID NO: 346; and SEQ ID NO: 348 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 341 or the variable light chain sequence of SEQ ID NO: 342 or sequences that are at least 90% or 95% identical thereto.

[0526] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 323; SEQ ID NO: 325; SEQ ID NO: 327; and SEQ ID NO: 329 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 321 or the variable heavy chain sequence of SEQ ID NO: 322 or sequences that are at least 90% or 95% identical thereto.

[0527] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 343; SEQ ID NO: 345; SEQ ID NO: 347; and SEQ ID NO: 349 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 341 or the variable light chain sequence of SEQ ID NO: 342 or sequences that are at least 90% or 95% identical thereto.

[0528] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 322; the variable light chain region of SEQ ID NO: 342; the complementarity-determining regions (SEQ ID NO: 324; SEQ ID NO: 326; and SEQ ID NO: 328) of the variable heavy chain region of SEQ ID NO: 322; and the complementarity-determining regions (SEQ ID NO: 344; SEQ ID NO: 346; and SEQ ID NO: 348) of the variable light chain region of SEQ ID NO: 342 or sequences that are at least 90% or 95% identical thereto.

[0529] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 322; the variable light chain region of SEQ ID NO: 342; the framework regions (SEQ ID NO: 323; SEQ ID NO: 325; SEQ ID NO: 327; and SEQ ID NO: 329) of the variable heavy chain region of SEQ ID NO: 322; and the framework regions (SEQ ID NO: 343; SEQ ID NO: 345; SEQ ID NO: 347; and SEQ ID NO: 349) of the variable light chain region of SEQ ID NO: 342.

[0530] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab10, comprising, or alternatively consisting of, SEQ ID NO: 321 and SEQ ID NO: 341 or SEQ ID NO: 322 and SEQ ID NO: 342, or an antibody or antibody fragment comprising the CDRs of Ab10 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab10 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab10 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab10.

[0531] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab10, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 322 and the variable light chain sequence of SEQ ID NO: 342 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 322 and/or SEQ ID NO: 342 which retain the binding specificity for ACTH.

[0532] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10. In another embodiment of the invention, anti-ACTH antibodies such as Ab10 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as

yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0533] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab10 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0534] Antibody Ab11

[0535] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSLEESGGRLVTPGTSLTLTCTASGFSLSAYDILWVRQAPGKGLESIGMMYDDGDTYYATW
AKGRFIISRTSTTMDLKIISPTTEDTATYFCVKGVSNIWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK (SEQ ID NO: 361).

[0536] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0537] QSLEESGGRLVTPGTSLTLTCTASGFSLSAYDILWVRQAPGKGLESIGMMYDDGD
TYYATWAKGRFIISRTSTTMDLKIISPTTEDTATYFCVKGVSNIWGQGTLVTVSS (SEQ ID NO:
362).

[0538] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab11 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 370).

[0539] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIVMTQIPASVEAAVGGTVTIKCQASQSIDSSLAWYQQKPGQPPKLLIYSASTLASGVPSRFK GSGSGTEFTLTIGDLECADAATYYCQSYDGSSSSYYGIGFGGGTEVVVKRTVAAPSVFIFPPSD EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 381).

[0540] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DIVMTQIPASVEAAVGGTVTIKCQASQSIDSSLAWYQQKPGQPPKLLIYSASTLASGVPSRFK GSGSGTEFTLTIGDLECADAATYYCQSYDGSSSSYYGIGFGGGTEVVVKR (SEQ ID NO: 382).

[0541] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab11 which contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 390).

[0542] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 366; and SEQ ID NO: 368 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 361 or which contain the variable heavy chain sequence of SEQ ID NO: 362, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 384; SEQ ID NO: 386; and SEQ ID NO: 388 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 381 or which contain the variable light chain sequence of SEQ ID NO: 382, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0543] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 363; SEQ ID NO: 365; SEQ ID NO: 367; and SEQ ID NO: 369 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 361 or the variable heavy chain sequence of SEQ ID NO: 362, and/or one, two, three, or four of the polypeptide sequences of SEQ ID

NO: 383; SEQ ID NO: 385; SEQ ID NO: 387; and SEQ ID NO: 389 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 381 or the variable light chain sequence of SEQ ID NO: 382, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0544] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0545] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 361 or SEQ ID NO: 362 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 381 or SEQ ID NO: 382 or polypeptides that are at least 90% or 95% identical thereto.

[0546] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 364; SEQ ID NO: 366; and SEQ ID NO: 368 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 361 or the variable heavy chain sequence of SEQ ID NO: 362 or sequences that are at least 90% or 95% identical thereto.

[0547] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 384; SEQ ID NO: 386; and SEQ ID NO: 388 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 381 or the variable light chain sequence of SEQ ID NO: 382 or sequences that are at least 90% or 95% identical thereto.

[0548] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 363; SEQ ID NO: 365; SEQ ID NO: 367; and SEQ ID NO: 369 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 361 or the variable heavy chain sequence of SEQ ID NO: 362 or sequences that are at least 90% or 95% identical thereto.

[0549] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 383; SEQ ID NO: 385; SEQ ID NO: 387; and SEQ ID NO:

389 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 381 or the variable light chain sequence of SEQ ID NO: 382 or sequences that are at least 90% or 95% identical thereto.

[0550] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 362; the variable light chain region of SEQ ID NO: 382; the complementarity-determining regions (SEQ ID NO: 364; SEQ ID NO: 366; and SEQ ID NO: 368) of the variable heavy chain region of SEQ ID NO: 362; and the complementarity-determining regions (SEQ ID NO: 384; SEQ ID NO: 386; and SEQ ID NO: 388) of the variable light chain region of SEQ ID NO: 382 or sequences that are at least 90% or 95% identical thereto.

[0551] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 362; the variable light chain region of SEQ ID NO: 382; the framework regions (SEQ ID NO: 363; SEQ ID NO: 365; SEQ ID NO: 367; and SEQ ID NO: 369) of the variable heavy chain region of SEQ ID NO: 362; and the framework regions (SEQ ID NO: 383; SEQ ID NO: 385; SEQ ID NO: 387; and SEQ ID NO: 389) of the variable light chain region of SEQ ID NO: 382.

[0552] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab11, comprising, or alternatively consisting of, SEQ ID NO: 361 and SEQ ID NO: 381 or SEQ ID NO: 362 and SEQ ID NO: 382, or an antibody or antibody fragment comprising the CDRs of Ab11 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab11 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab11 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab11.

[0553] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab11, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 362 and the variable light chain sequence of SEQ ID NO: 382 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 362 and/or SEQ ID NO: 382 which retain the binding specificity for ACTH.

[0554] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab11. In another embodiment of the invention,

anti-ACTH antibodies such as Ab11 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0555] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab11 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0556] Antibody Ab12

[0557] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

QSVEESGGRLVTPGTPLTLTCTVSGSSLSDYDMIWVRQAPGKGLESIGIIYDDGDTYYATWA
KGRFTISKTSTTVDLRIISPTTEDTATYFCVKGVSNMWGPGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEY
KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK (SEQ ID NO: 401).

[0558] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0559] QSVEESGGRLVTPGTPLTLTCTVSGSSLSDYDMIWVRQAPGKGLESIGIIYDDGDT
YYATWAKGRFTISKTSTTVDLRIISPTTEDTATYFCVKGVSNMWGPGTLVTVSS (SEQ ID NO:
402).

[0560] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab12 and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC

LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 410).

[0561] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DVVMTQTPSSVSAAVGGTVTIKCQASQSIGSSLAWYQQKPGQRPKLLIYAASTLASGVPSRF KGSGSGTEFTLTISDLECADAATYYCQSYDGSSSSSYGVGFGGGTEVVVKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 421).

[0562] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DVVMTQTPSSVSAAVGGTVTIKCQASQSIGSSLAWYQQKPGQRPKLLIYAASTLASGVPSRF KGSGSGTEFTLTISDLECADAATYYCQSYDGSSSSSYGVGFGGGTEVVVKR (SEQ ID NO: 422).

[0563] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab12 which contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 430).

[0564] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 404; SEQ ID NO: 406; and SEQ ID NO: 408 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 401 or which contain the variable heavy chain sequence of SEQ ID NO: 402, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 424; SEQ ID NO: 426; and SEQ ID NO: 428 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 421 or which contain the variable light chain sequence of SEQ ID NO: 422, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0565] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 403; SEQ ID NO:

405; SEQ ID NO: 407; and SEQ ID NO: 409 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 401 or the variable heavy chain sequence of SEQ ID NO: 402, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 423; SEQ ID NO: 425; SEQ ID NO: 427; and SEQ ID NO: 429 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 421 or the variable light chain sequence of SEQ ID NO: 422, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0566] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0567] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 401 or SEQ ID NO: 402 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 421 or SEQ ID NO: 422 or polypeptides that are at least 90% or 95% identical thereto.

[0568] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 404; SEQ ID NO: 406; and SEQ ID NO: 408 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 401 or the variable heavy chain sequence of SEQ ID NO: 402 or sequences that are at least 90% or 95% identical thereto.

[0569] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 424; SEQ ID NO: 426; and SEQ ID NO: 428 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 421 or the variable light chain sequence of SEQ ID NO: 422 or sequences that are at least 90% or 95% identical thereto.

[0570] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 403; SEQ ID NO: 405; SEQ ID NO: 407; and SEQ ID NO: 409 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 401 or the variable heavy chain sequence of SEQ ID NO: 402 or sequences that are at least 90% or 95% identical thereto.

[0571] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 423; SEQ ID NO: 425; SEQ ID NO: 427; and SEQ ID NO: 429 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 421 or the variable light chain sequence of SEQ ID NO: 422 or sequences that are at least 90% or 95% identical thereto.

[0572] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 402; the variable light chain region of SEQ ID NO: 422; the complementarity-determining regions (SEQ ID NO: 404; SEQ ID NO: 406; and SEQ ID NO: 408) of the variable heavy chain region of SEQ ID NO: 402; and the complementarity-determining regions (SEQ ID NO: 424; SEQ ID NO: 426; and SEQ ID NO: 428) of the variable light chain region of SEQ ID NO: 422 or sequences that are at least 90% or 95% identical thereto.

[0573] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 402; the variable light chain region of SEQ ID NO: 422; the framework regions (SEQ ID NO: 403; SEQ ID NO: 405; SEQ ID NO: 407; and SEQ ID NO: 409) of the variable heavy chain region of SEQ ID NO: 402; and the framework regions (SEQ ID NO: 423; SEQ ID NO: 425; SEQ ID NO: 427; and SEQ ID NO: 429) of the variable light chain region of SEQ ID NO: 422.

[0574] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab12, comprising, or alternatively consisting of, SEQ ID NO: 401 and SEQ ID NO: 421 or SEQ ID NO: 402 and SEQ ID NO: 422, or an antibody or antibody fragment comprising the CDRs of Ab12 and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab12 in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab12 or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab12.

[0575] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab12, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 402 and the variable light chain sequence of SEQ ID NO: 422 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This

embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 402 and/or SEQ ID NO: 422 which retain the binding specificity for ACTH.

[0576] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab12. In another embodiment of the invention, anti-ACTH antibodies such as Ab12 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0577] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab12 as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0578] Antibody Ab1.H

[0579] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGFTVSNYDMIWVRQAPGKGLESIGMIYDDGDTYYAS
SAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNHWGQGTLVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 441).

[0580] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0581] EVQLVESGGGLVQPGGSLRLSCAASGFTVSNYDMIWVRQAPGKGLESIGMIYDDG
DTYYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNHWGQGTLVTVSS
(SEQ ID NO: 442).

[0582] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab1.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY

SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 450).

[0583] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSISSYLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYDGSSGSSYGVGFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 461).

[0584] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSISSYLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYDGSSGSSYGVGFGGGTKVEIKR (SEQ ID NO: 462).

[0585] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab1.H which contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 470).

[0586] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 446; and SEQ ID NO: 448 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 441 or which contain the variable heavy chain sequence of SEQ ID NO: 442, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 464; SEQ ID NO: 466; and SEQ ID NO: 468 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 461 or which contain the variable light chain sequence of SEQ ID NO: 462, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0587] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 443; SEQ ID NO: 445; SEQ ID NO: 447; and SEQ ID NO: 449 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 441 or the variable heavy chain sequence of SEQ ID NO: 442, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 465; SEQ ID NO: 467; and SEQ ID NO: 469 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 461 or the variable light chain sequence of SEQ ID NO: 462, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0588] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0589] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 441 or SEQ ID NO: 442 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 461 or SEQ ID NO: 462 or polypeptides that are at least 90% or 95% identical thereto.

[0590] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 444; SEQ ID NO: 446; and SEQ ID NO: 448 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 441 or the variable heavy chain sequence of SEQ ID NO: 442 or sequences that are at least 90% or 95% identical thereto.

[0591] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 464; SEQ ID NO: 466; and SEQ ID NO: 468 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 461 or the variable light chain sequence of SEQ ID NO: 462 or sequences that are at least 90% or 95% identical thereto.

[0592] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 443; SEQ ID NO: 445; SEQ ID NO: 447; and SEQ ID NO: 449 which correspond to the framework regions (FRs or constant regions) of the heavy chain

sequence of SEQ ID NO: 441 or the variable heavy chain sequence of SEQ ID NO: 442 or sequences that are at least 90% or 95% identical thereto.

[0593] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 463; SEQ ID NO: 465; SEQ ID NO: 467; and SEQ ID NO: 469 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 461 or the variable light chain sequence of SEQ ID NO: 462 or sequences that are at least 90% or 95% identical thereto.

[0594] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 442; the variable light chain region of SEQ ID NO: 462; the complementarity-determining regions (SEQ ID NO: 444; SEQ ID NO: 446; and SEQ ID NO: 448) of the variable heavy chain region of SEQ ID NO: 442; and the complementarity-determining regions (SEQ ID NO: 464; SEQ ID NO: 466; and SEQ ID NO: 468) of the variable light chain region of SEQ ID NO: 462 or sequences that are at least 90% or 95% identical thereto.

[0595] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 442; the variable light chain region of SEQ ID NO: 462; the framework regions (SEQ ID NO: 443; SEQ ID NO: 445; SEQ ID NO: 447; and SEQ ID NO: 449) of the variable heavy chain region of SEQ ID NO: 442; and the framework regions (SEQ ID NO: 463; SEQ ID NO: 465; SEQ ID NO: 467; and SEQ ID NO: 469) of the variable light chain region of SEQ ID NO: 462.

[0596] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab1.H, comprising, or alternatively consisting of, SEQ ID NO: 441 and SEQ ID NO: 461 or SEQ ID NO: 442 and SEQ ID NO: 462, or an antibody or antibody fragment comprising the CDRs of Ab1.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab1.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab1.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab1.H.

[0597] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab1.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 442 and the variable light chain sequence of SEQ ID

NO: 462 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 442 and/or SEQ ID NO: 462 which retain the binding specificity for ACTH.

[0598] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab1.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab1.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0599] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab1.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0600] Antibody Ab2.H

[0601] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGFTVSKYDMIWVRQAPGKGLESIGIIYDDGDTYYASS
AKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS
SLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 481).

[0602] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0603] EVQLVESGGGLVQPGGSLRLSCAASGFTVSKYDMIWVRQAPGKGLESIGIIYDDG
DTYYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSS (SEQ ID NO: 482).

[0604] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab2.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 490).

[0605] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSISNYLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYEGSSSSSYGVGFGGGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 501).

[0606] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSISNYLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYEGSSSSSYGVGFGGGTKVEIKR (SEQ ID NO: 502).

[0607] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab2.H which contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 510).

[0608] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 484; SEQ ID NO: 486; and SEQ ID NO: 488 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 481 or which contain the variable heavy chain sequence of SEQ ID NO: 482, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 504; SEQ ID NO: 506; and SEQ ID NO: 508 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 501 or which contain the variable light chain sequence of SEQ ID NO: 502, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and

variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0609] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 483; SEQ ID NO: 485; SEQ ID NO: 487; and SEQ ID NO: 489 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 481 or the variable heavy chain sequence of SEQ ID NO: 482, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 503; SEQ ID NO: 505; SEQ ID NO: 507; and SEQ ID NO: 509 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 501 or the variable light chain sequence of SEQ ID NO: 502, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0610] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0611] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 481 or SEQ ID NO: 482 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 501 or SEQ ID NO: 502 or polypeptides that are at least 90% or 95% identical thereto.

[0612] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 484; SEQ ID NO: 486; and SEQ ID NO: 488 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 481 or the variable heavy chain sequence of SEQ ID NO: 482 or sequences that are at least 90% or 95% identical thereto.

[0613] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 504; SEQ ID NO: 506; and SEQ ID NO: 508 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 501 or the variable light chain sequence of SEQ ID NO: 502 or sequences that are at least 90% or 95% identical thereto.

[0614] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the

polypeptide sequences of SEQ ID NO: 483; SEQ ID NO: 485; SEQ ID NO: 487; and SEQ ID NO: 489 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 481 or the variable heavy chain sequence of SEQ ID NO: 482 or sequences that are at least 90% or 95% identical thereto.

[0615] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 503; SEQ ID NO: 505; SEQ ID NO: 507; and SEQ ID NO: 509 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 501 or the variable light chain sequence of SEQ ID NO: 502 or sequences that are at least 90% or 95% identical thereto.

[0616] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 482; the variable light chain region of SEQ ID NO: 502; the complementarity-determining regions (SEQ ID NO: 484; SEQ ID NO: 486; and SEQ ID NO: 488) of the variable heavy chain region of SEQ ID NO: 482; and the complementarity-determining regions (SEQ ID NO: 504; SEQ ID NO: 506; and SEQ ID NO: 508) of the variable light chain region of SEQ ID NO: 502 or sequences that are at least 90% or 95% identical thereto.

[0617] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 482; the variable light chain region of SEQ ID NO: 502; the framework regions (SEQ ID NO: 483; SEQ ID NO: 485; SEQ ID NO: 487; and SEQ ID NO: 489) of the variable heavy chain region of SEQ ID NO: 482; and the framework regions (SEQ ID NO: 503; SEQ ID NO: 505; SEQ ID NO: 507; and SEQ ID NO: 509) of the variable light chain region of SEQ ID NO: 502.

[0618] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab2.H, comprising, or alternatively consisting of, SEQ ID NO: 481 and SEQ ID NO: 501 or SEQ ID NO: 482 and SEQ ID NO: 502, or an antibody or antibody fragment comprising the CDRs of Ab2.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab2.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab2.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab2.H.

[0619] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding

specificity for ACTH. With respect to antibody Ab2.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 482 and the variable light chain sequence of SEQ ID NO: 502 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 482 and/or SEQ ID NO: 502 which retain the binding specificity for ACTH.

[0620] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab2.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab2.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0621] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab2.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0622] Antibody Ab3.H

[0623] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGSSLSNFDMIWVRQAPGKGLESIGIIYDFGSTYYASSA
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSSASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS
LGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 521).

[0624] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0625] EVQLVESGGGLVQPGGSLRLSCAASGSSLSNFDMIWVRQAPGKGLESIGIIYDFGS
TYYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSS (SEQ
ID NO: 522).

[0626] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab3.H and which contain a

constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 530).

[0627] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:
DIQMTQSPSTLSASVGDRVTITCQASEDISSNLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG
SGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSSYGIGFGGGTKVEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 541).

[0628] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:
DIQMTQSPSTLSASVGDRVTITCQASEDISSNLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG
SGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSSYGIGFGGGTKVEIKR (SEQ ID NO: 542).

[0629] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab3.H which contain a constant light chain sequence comprising the sequence set forth below:
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD
STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 550).

[0630] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 526; and SEQ ID NO: 528 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 521 or which contain the variable heavy chain sequence of SEQ ID NO: 522, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 544; SEQ ID NO: 546; and SEQ ID NO: 548 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 541 or which contain the variable light chain sequence of SEQ ID NO: 542, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise,

or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0631] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 523; SEQ ID NO: 525; SEQ ID NO: 527; and SEQ ID NO: 529 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 521 or the variable heavy chain sequence of SEQ ID NO: 522, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 545; SEQ ID NO: 547; and SEQ ID NO: 549 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 541 or the variable light chain sequence of SEQ ID NO: 542, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0632] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0633] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 521 or SEQ ID NO: 522 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 541 or SEQ ID NO: 542 or polypeptides that are at least 90% or 95% identical thereto.

[0634] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 524; SEQ ID NO: 526; and SEQ ID NO: 528 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 521 or the variable heavy chain sequence of SEQ ID NO: 522 or sequences that are at least 90% or 95% identical thereto.

[0635] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 544; SEQ ID NO: 546; and SEQ ID NO: 548 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 541 or the variable light chain sequence of SEQ ID NO: 542 or sequences that are at least 90% or 95% identical thereto.

[0636] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 523; SEQ ID NO: 525; SEQ ID NO: 527; and SEQ ID NO: 529 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 521 or the variable heavy chain sequence of SEQ ID NO: 522 or sequences that are at least 90% or 95% identical thereto.

[0637] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 543; SEQ ID NO: 545; SEQ ID NO: 547; and SEQ ID NO: 549 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 541 or the variable light chain sequence of SEQ ID NO: 542 or sequences that are at least 90% or 95% identical thereto.

[0638] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 522; the variable light chain region of SEQ ID NO: 542; the complementarity-determining regions (SEQ ID NO: 524; SEQ ID NO: 526; and SEQ ID NO: 528) of the variable heavy chain region of SEQ ID NO: 522; and the complementarity-determining regions (SEQ ID NO: 544; SEQ ID NO: 546; and SEQ ID NO: 548) of the variable light chain region of SEQ ID NO: 542 or sequences that are at least 90% or 95% identical thereto.

[0639] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 522; the variable light chain region of SEQ ID NO: 542; the framework regions (SEQ ID NO: 523; SEQ ID NO: 525; SEQ ID NO: 527; and SEQ ID NO: 529) of the variable heavy chain region of SEQ ID NO: 522; and the framework regions (SEQ ID NO: 543; SEQ ID NO: 545; SEQ ID NO: 547; and SEQ ID NO: 549) of the variable light chain region of SEQ ID NO: 542.

[0640] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab3.H, comprising, or alternatively consisting of, SEQ ID NO: 521 and SEQ ID NO: 541 or SEQ ID NO: 522 and SEQ ID NO: 542, or an antibody or antibody fragment comprising the CDRs of Ab3.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab3.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab3.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab3.H.

[0641] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab3.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 522 and the variable light chain sequence of SEQ ID NO: 542 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 522 and/or SEQ ID NO: 542 which retain the binding specificity for ACTH.

[0642] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab3.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab3.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0643] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab3.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0644] Antibody Ab4.H

[0645] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGFTVSKHDMIWVRQAPGKGLESIGIIYDDGDTYYANS
AKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS
SLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 561).

[0646] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0647] EVQLVESGGGLVQPGGSLRLSCAASGFTVSKHDMIWVRQAPGKGLESIGIIYDDG
DTYYANSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSS
(SEQ ID NO: 562).

[0648] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab4.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 570).

[0649] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:
DIQMTQSPSTLSASVGDRVTITCRASQSISVYLAWYQQKPGKAPKLLIYQASKLASGVPSRFS GSGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSSYGVGFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 581).

[0650] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:
DIQMTQSPSTLSASVGDRVTITCRASQSISVYLAWYQQKPGKAPKLLIYQASKLASGVPSRFS GSGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSSYGVGFGGGTKVEIKR (SEQ ID NO: 582).

[0651] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab4.H which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 590).

[0652] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 564; SEQ ID NO: 566; and SEQ ID NO: 568 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 561 or which contain the variable heavy chain sequence of SEQ ID NO: 562, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 584; SEQ ID NO: 586; and SEQ ID NO: 588 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 581 or which contain the variable light chain sequence of SEQ ID NO: 582, or antibodies or fragments containing combinations of

sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0653] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 563; SEQ ID NO: 565; SEQ ID NO: 567; and SEQ ID NO: 569 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 561 or the variable heavy chain sequence of SEQ ID NO: 562, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 583; SEQ ID NO: 585; SEQ ID NO: 587; and SEQ ID NO: 589 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 581 or the variable light chain sequence of SEQ ID NO: 582, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0654] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0655] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 561 or SEQ ID NO: 562 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 581 or SEQ ID NO: 582 or polypeptides that are at least 90% or 95% identical thereto.

[0656] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 564; SEQ ID NO: 566; and SEQ ID NO: 568 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 561 or the variable heavy chain sequence of SEQ ID NO: 562 or sequences that are at least 90% or 95% identical thereto.

[0657] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 584; SEQ ID NO: 586; and SEQ ID NO: 588 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light

chain sequence of SEQ ID NO: 581 or the variable light chain sequence of SEQ ID NO: 582 or sequences that are at least 90% or 95% identical thereto.

[0658] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 563; SEQ ID NO: 565; SEQ ID NO: 567; and SEQ ID NO: 569 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 561 or the variable heavy chain sequence of SEQ ID NO: 562 or sequences that are at least 90% or 95% identical thereto.

[0659] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 583; SEQ ID NO: 585; SEQ ID NO: 587; and SEQ ID NO: 589 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 581 or the variable light chain sequence of SEQ ID NO: 582 or sequences that are at least 90% or 95% identical thereto.

[0660] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 562; the variable light chain region of SEQ ID NO: 582; the complementarity-determining regions (SEQ ID NO: 564; SEQ ID NO: 566; and SEQ ID NO: 568) of the variable heavy chain region of SEQ ID NO: 562; and the complementarity-determining regions (SEQ ID NO: 584; SEQ ID NO: 586; and SEQ ID NO: 588) of the variable light chain region of SEQ ID NO: 582 or sequences that are at least 90% or 95% identical thereto.

[0661] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 562; the variable light chain region of SEQ ID NO: 582; the framework regions (SEQ ID NO: 563; SEQ ID NO: 565; SEQ ID NO: 567; and SEQ ID NO: 569) of the variable heavy chain region of SEQ ID NO: 562; and the framework regions (SEQ ID NO: 583; SEQ ID NO: 585; SEQ ID NO: 587; and SEQ ID NO: 589) of the variable light chain region of SEQ ID NO: 582.

[0662] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab4.H, comprising, or alternatively consisting of, SEQ ID NO: 561 and SEQ ID NO: 581 or SEQ ID NO: 562 and SEQ ID NO: 582, or an antibody or antibody fragment comprising the CDRs of Ab4.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab4.H in binding ACTH, preferably one containing sequences that are at least 90%,

95%, 96%, 97%, 98% or 99% identical to that of Ab4.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab4.H.

[0663] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab4.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 562 and the variable light chain sequence of SEQ ID NO: 582 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 562 and/or SEQ ID NO: 582 which retain the binding specificity for ACTH.

[0664] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab4.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab4.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0665] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab4.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0666] Antibody Ab6.H

[0667] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGFSLTDYAMSWVRQAPGKGLEWIGIISDSGSTYYASS
AKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPEYGYDEYGDWVSDLWGQGTLVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFL
FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 601).

[0668] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0669] EVQLVESGGGLVQPGGSLRLSCAASGFSLTDYAMSWVRQAPGKGLEWIGIISDSG STYYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPEYGYDEYGDWVSDLWG QGTLVTVSS (SEQ ID NO: 602).

[0670] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab6.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 610).

[0671] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQATQSIGNNLAWYQQKPGKAPKLLIYRASTLASGVPSRFS GSGSGTEFTLTISSLQPDDFATYYCQSYYYSSSITYHNAFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 621).

[0672] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQATQSIGNNLAWYQQKPGKAPKLLIYRASTLASGVPSRFS GSGSGTEFTLTISSLQPDDFATYYCQSYYYSSSITYHNAFGGGTKVEIKR (SEQ ID NO: 622).

[0673] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab6.H which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 630).

[0674] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 604; SEQ ID NO: 606; and SEQ ID NO: 608 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 601 or which contain the variable heavy chain sequence of SEQ ID NO: 602, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 624; SEQ ID NO: 626; and

SEQ ID NO: 628 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 621 or which contain the variable light chain sequence of SEQ ID NO: 622, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0675] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 603; SEQ ID NO: 605; SEQ ID NO: 607; and SEQ ID NO: 609 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 601 or the variable heavy chain sequence of SEQ ID NO: 602, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 623; SEQ ID NO: 625; SEQ ID NO: 627; and SEQ ID NO: 629 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 621 or the variable light chain sequence of SEQ ID NO: 622, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0676] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0677] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 601 or SEQ ID NO: 602 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 621 or SEQ ID NO: 622 or polypeptides that are at least 90% or 95% identical thereto.

[0678] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 604; SEQ ID NO: 606; and SEQ ID NO: 608 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 601 or the variable heavy chain sequence of SEQ ID NO: 602 or sequences that are at least 90% or 95% identical thereto.

[0679] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the

polypeptide sequences of SEQ ID NO: 624; SEQ ID NO: 626; and SEQ ID NO: 628 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 621 or the variable light chain sequence of SEQ ID NO: 622 or sequences that are at least 90% or 95% identical thereto.

[0680] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 603; SEQ ID NO: 605; SEQ ID NO: 607; and SEQ ID NO: 609 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 601 or the variable heavy chain sequence of SEQ ID NO: 602 or sequences that are at least 90% or 95% identical thereto.

[0681] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 623; SEQ ID NO: 625; SEQ ID NO: 627; and SEQ ID NO: 629 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 621 or the variable light chain sequence of SEQ ID NO: 622 or sequences that are at least 90% or 95% identical thereto.

[0682] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 602; the variable light chain region of SEQ ID NO: 622; the complementarity-determining regions (SEQ ID NO: 604; SEQ ID NO: 606; and SEQ ID NO: 608) of the variable heavy chain region of SEQ ID NO: 602; and the complementarity-determining regions (SEQ ID NO: 624; SEQ ID NO: 626; and SEQ ID NO: 628) of the variable light chain region of SEQ ID NO: 622 or sequences that are at least 90% or 95% identical thereto.

[0683] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 602; the variable light chain region of SEQ ID NO: 622; the framework regions (SEQ ID NO: 603; SEQ ID NO: 605; SEQ ID NO: 607; and SEQ ID NO: 609) of the variable heavy chain region of SEQ ID NO: 602; and the framework regions (SEQ ID NO: 623; SEQ ID NO: 625; SEQ ID NO: 627; and SEQ ID NO: 629) of the variable light chain region of SEQ ID NO: 622.

[0684] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab6.H, comprising, or alternatively consisting of, SEQ ID NO: 601 and SEQ ID NO: 621 or SEQ ID NO: 602 and SEQ ID NO: 622, or an antibody or antibody fragment comprising the CDRs of Ab6.H and

having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab6.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab6.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab6.H.

[0685] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab6.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 602 and the variable light chain sequence of SEQ ID NO: 622 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 602 and/or SEQ ID NO: 622 which retain the binding specificity for ACTH.

[0686] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab6.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0687] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab6.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0688] Antibody Ab7.H

[0689] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGFSLSSYAMSWVRQAPGKGLEWIGIISDSGSTYYASSA
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPEYGYDDYGDWVSDLWGQGTLVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV
MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 641).

[0690] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0691] EVQLVESGGGLVQPGGSLRLSCAASGFSLSSYAMSWVRQAPGKGLEWIGIISDSGS TYYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPEYGYDDYGDWVSDLWGQ GTLVTVSS (SEQ ID NO: 642).

[0692] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab7.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 650).

[0693] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSISDYLSWYQQKPGKAPKLLIYRASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYYYSSSITYRNAFGGGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 661).

[0694] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSISDYLSWYQQKPGKAPKLLIYRASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYYYSSSITYRNAFGGGTKVEIKR (SEQ ID NO: 662).

[0695] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab7.H which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 670).

[0696] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 644; SEQ ID NO: 646; and SEQ ID NO: 648 which correspond to the complementarity-

determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 641 or which contain the variable heavy chain sequence of SEQ ID NO: 642, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 664; SEQ ID NO: 666; and SEQ ID NO: 668 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 661 or which contain the variable light chain sequence of SEQ ID NO: 662, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0697] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 643; SEQ ID NO: 645; SEQ ID NO: 647; and SEQ ID NO: 649 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 641 or the variable heavy chain sequence of SEQ ID NO: 642, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 663; SEQ ID NO: 665; SEQ ID NO: 667; and SEQ ID NO: 669 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 661 or the variable light chain sequence of SEQ ID NO: 662, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0698] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0699] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 641 or SEQ ID NO: 642 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 661 or SEQ ID NO: 662 or polypeptides that are at least 90% or 95% identical thereto.

[0700] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 644; SEQ ID NO: 646; and SEQ ID NO: 648 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the

heavy chain sequence of SEQ ID NO: 641 or the variable heavy chain sequence of SEQ ID NO: 642 or sequences that are at least 90% or 95% identical thereto.

[0701] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 664; SEQ ID NO: 666; and SEQ ID NO: 668 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 661 or the variable light chain sequence of SEQ ID NO: 662 or sequences that are at least 90% or 95% identical thereto.

[0702] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 643; SEQ ID NO: 645; SEQ ID NO: 647; and SEQ ID NO: 649 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 641 or the variable heavy chain sequence of SEQ ID NO: 642 or sequences that are at least 90% or 95% identical thereto.

[0703] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 663; SEQ ID NO: 665; SEQ ID NO: 667; and SEQ ID NO: 669 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 661 or the variable light chain sequence of SEQ ID NO: 662 or sequences that are at least 90% or 95% identical thereto.

[0704] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 642; the variable light chain region of SEQ ID NO: 662; the complementarity-determining regions (SEQ ID NO: 644; SEQ ID NO: 646; and SEQ ID NO: 648) of the variable heavy chain region of SEQ ID NO: 642; and the complementarity-determining regions (SEQ ID NO: 664; SEQ ID NO: 666; and SEQ ID NO: 668) of the variable light chain region of SEQ ID NO: 662 or sequences that are at least 90% or 95% identical thereto.

[0705] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 642; the variable light chain region of SEQ ID NO: 662; the framework regions (SEQ ID NO: 643; SEQ ID NO: 645; SEQ ID NO: 647; and SEQ ID NO: 649) of the variable heavy chain region of

SEQ ID NO: 642; and the framework regions (SEQ ID NO: 663; SEQ ID NO: 665; SEQ ID NO: 667; and SEQ ID NO: 669) of the variable light chain region of SEQ ID NO: 662.

[0706] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab7.H, comprising, or alternatively consisting of, SEQ ID NO: 641 and SEQ ID NO: 661 or SEQ ID NO: 642 and SEQ ID NO: 662, or an antibody or antibody fragment comprising the CDRs of Ab7.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab7.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab7.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab7.H.

[0707] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab7.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 642 and the variable light chain sequence of SEQ ID NO: 662 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 642 and/or SEQ ID NO: 662 which retain the binding specificity for ACTH.

[0708] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab7.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab7.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0709] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab7.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0710] Antibody Ab7A.H

[0711] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGFSLSSYAMSWVRQAPGKGLEWIGIISDSGSTYYASSA
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPEYGYDDYGDWVSDLWGQGTLVTVS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVS

VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 681).

[0712] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0713] EVQLVESGGGLVQPGGSLRLSCAASGFSLSSYAMSWVRQAPGKGLEWIGIISDSGS TYYASSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREPEYGYDDYGDWVSDLWGQ GTLVTVSS (SEQ ID NO: 682).

[0714] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab7A.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 690).

[0715] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

ADIQMTQSPSTLSASVGDRVTITCQASQSISDYLSWYQQKPGKAPKLLIYRASTLASGVPSRFS GSGSGTEFTLTISSLQPDDFATYYCQSYYYSSSITYRNAFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 701).

[0716] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

ADIQMTQSPSTLSASVGDRVTITCQASQSISDYLSWYQQKPGKAPKLLIYRASTLASGVPSRFS GSGSGTEFTLTISSLQPDDFATYYCQSYYYSSSITYRNAFGGGTKVEIKR (SEQ ID NO: 702).

[0717] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab7A.H which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 710).

[0718] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 684; SEQ ID NO: 686; and SEQ ID NO: 688 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 681 or which contain the variable heavy chain sequence of SEQ ID NO: 682, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 704; SEQ ID NO: 706; and SEQ ID NO: 708 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 701 or which contain the variable light chain sequence of SEQ ID NO: 702, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0719] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 683; SEQ ID NO: 685; SEQ ID NO: 687; and SEQ ID NO: 689 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 681 or the variable heavy chain sequence of SEQ ID NO: 682, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 703; SEQ ID NO: 705; SEQ ID NO: 707; and SEQ ID NO: 709 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 701 or the variable light chain sequence of SEQ ID NO: 702, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0720] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0721] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 681 or SEQ ID NO: 682 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 701 or SEQ ID NO: 702 or polypeptides that are at least 90% or 95% identical thereto.

[0722] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the

polypeptide sequences of SEQ ID NO: 684; SEQ ID NO: 686; and SEQ ID NO: 688 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 681 or the variable heavy chain sequence of SEQ ID NO: 682 or sequences that are at least 90% or 95% identical thereto.

[0723] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 704; SEQ ID NO: 706; and SEQ ID NO: 708 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 701 or the variable light chain sequence of SEQ ID NO: 702 or sequences that are at least 90% or 95% identical thereto.

[0724] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 683; SEQ ID NO: 685; SEQ ID NO: 687; and SEQ ID NO: 689 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 681 or the variable heavy chain sequence of SEQ ID NO: 682 or sequences that are at least 90% or 95% identical thereto.

[0725] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 703; SEQ ID NO: 705; SEQ ID NO: 707; and SEQ ID NO: 709 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 701 or the variable light chain sequence of SEQ ID NO: 702 or sequences that are at least 90% or 95% identical thereto.

[0726] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 682; the variable light chain region of SEQ ID NO: 702; the complementarity-determining regions (SEQ ID NO: 684; SEQ ID NO: 686; and SEQ ID NO: 688) of the variable heavy chain region of SEQ ID NO: 682; and the complementarity-determining regions (SEQ ID NO: 704; SEQ ID NO: 706; and SEQ ID NO: 708) of the variable light chain region of SEQ ID NO: 702 or sequences that are at least 90% or 95% identical thereto.

[0727] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 682; the variable light chain region of SEQ ID NO: 702; the framework regions (SEQ ID NO:

683; SEQ ID NO: 685; SEQ ID NO: 687; and SEQ ID NO: 689) of the variable heavy chain region of SEQ ID NO: 682; and the framework regions (SEQ ID NO: 703; SEQ ID NO: 705; SEQ ID NO: 707; and SEQ ID NO: 709) of the variable light chain region of SEQ ID NO: 702.

[0728] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab7A.H, comprising, or alternatively consisting of, SEQ ID NO: 681 and SEQ ID NO: 701 or SEQ ID NO: 682 and SEQ ID NO: 702, or an antibody or antibody fragment comprising the CDRs of Ab7A.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab7A.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab7A.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab7A.H.

[0729] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab7A.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 682 and the variable light chain sequence of SEQ ID NO: 702 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 682 and/or SEQ ID NO: 702 which retain the binding specificity for ACTH.

[0730] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab7A.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab7A.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0731] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab7A.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0732] Antibody Ab10.H

[0733] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGFTVSSADMIWVRQAPGKGLESIGMIYDDGDTYYATS
AKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSSVWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS
SSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS

RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK (SEQ ID NO: 721).

[0734] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0735] EVQLVESGGGLVQPGGSLRLSCAASGFTVSSADMIWVRQAPGKGLESIGMIYDDG DTYYATSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSSVWGQGTLVTVSS (SEQ ID NO: 722).

[0736] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab10.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 730).

[0737] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASENIYRSLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSSYGVGFGGGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 741).

[0738] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASENIYRSLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSSYGVGFGGGTKVEIKR (SEQ ID NO: 742).

[0739] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab10.H which contain a constant light chain sequence comprising the sequence set forth below:

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 750).

[0740] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 724; SEQ ID NO: 726; and SEQ ID NO: 728 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 721 or which contain the variable heavy chain sequence of SEQ ID NO: 722, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 744; SEQ ID NO: 746; and SEQ ID NO: 748 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 741 or which contain the variable light chain sequence of SEQ ID NO: 742, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0741] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 723; SEQ ID NO: 725; SEQ ID NO: 727; and SEQ ID NO: 729 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 721 or the variable heavy chain sequence of SEQ ID NO: 722, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 743; SEQ ID NO: 745; SEQ ID NO: 747; and SEQ ID NO: 749 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 741 or the variable light chain sequence of SEQ ID NO: 742, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0742] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0743] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 721 or SEQ ID NO: 722 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 741 or SEQ ID NO: 742 or polypeptides that are at least 90% or 95% identical thereto.

[0744] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 724; SEQ ID NO: 726; and SEQ ID NO: 728 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 721 or the variable heavy chain sequence of SEQ ID NO: 722 or sequences that are at least 90% or 95% identical thereto.

[0745] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 744; SEQ ID NO: 746; and SEQ ID NO: 748 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 741 or the variable light chain sequence of SEQ ID NO: 742 or sequences that are at least 90% or 95% identical thereto.

[0746] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 723; SEQ ID NO: 725; SEQ ID NO: 727; and SEQ ID NO: 729 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 721 or the variable heavy chain sequence of SEQ ID NO: 722 or sequences that are at least 90% or 95% identical thereto.

[0747] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 743; SEQ ID NO: 745; SEQ ID NO: 747; and SEQ ID NO: 749 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 741 or the variable light chain sequence of SEQ ID NO: 742 or sequences that are at least 90% or 95% identical thereto.

[0748] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 722; the variable light chain region of SEQ ID NO: 742; the complementarity-determining regions (SEQ ID NO: 724; SEQ ID NO: 726; and SEQ ID NO: 728) of the variable heavy chain region of SEQ ID NO: 722; and the complementarity-determining regions (SEQ ID NO: 744; SEQ ID NO: 746; and SEQ ID NO: 748) of the variable light chain region of SEQ ID NO: 742 or sequences that are at least 90% or 95% identical thereto.

[0749] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or

more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 722; the variable light chain region of SEQ ID NO: 742; the framework regions (SEQ ID NO: 723; SEQ ID NO: 725; SEQ ID NO: 727; and SEQ ID NO: 729) of the variable heavy chain region of SEQ ID NO: 722; and the framework regions (SEQ ID NO: 743; SEQ ID NO: 745; SEQ ID NO: 747; and SEQ ID NO: 749) of the variable light chain region of SEQ ID NO: 742.

[0750] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab10.H, comprising, or alternatively consisting of, SEQ ID NO: 721 and SEQ ID NO: 741 or SEQ ID NO: 722 and SEQ ID NO: 742, or an antibody or antibody fragment comprising the CDRs of Ab10.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab10.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab10.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab10.H.

[0751] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab10.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 722 and the variable light chain sequence of SEQ ID NO: 742 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 722 and/or SEQ ID NO: 742 which retain the binding specificity for ACTH.

[0752] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab10.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0753] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab10.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0754] Antibody Ab11.H

[0755] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGFTVSAYDILWVRQAPGKGLESIGMMYDDGDTYYAT
SAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSSASTKGPSVFP

LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK (SEQ ID NO: 761).

[0756] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0757] EVQLVESGGGLVQPGGSLRLSCAASGFTVSAYDILWVRQAPGKGLESIGMMYDD GDTYYATSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSS (SEQ ID NO: 762).

[0758] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab11.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below: ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK (SEQ ID NO: 770).

[0759] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSIDSSLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSYYGIGFGGGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 781).

[0760] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSIDSSLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSYYGIGFGGGTKVEIKR (SEQ ID NO: 782).

[0761] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab11.H which contain a constant light

chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 790).

[0762] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 764; SEQ ID NO: 766; and SEQ ID NO: 768 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 761 or which contain the variable heavy chain sequence of SEQ ID NO: 762, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 784; SEQ ID NO: 786; and SEQ ID NO: 788 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 781 or which contain the variable light chain sequence of SEQ ID NO: 782, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0763] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 763; SEQ ID NO: 765; SEQ ID NO: 767; and SEQ ID NO: 769 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 761 or the variable heavy chain sequence of SEQ ID NO: 762, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 783; SEQ ID NO: 785; SEQ ID NO: 787; and SEQ ID NO: 789 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 781 or the variable light chain sequence of SEQ ID NO: 782, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0764] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0765] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 761 or SEQ ID NO: 762 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or

alternatively consist of, the polypeptide sequence of SEQ ID NO: 781 or SEQ ID NO: 782 or polypeptides that are at least 90% or 95% identical thereto.

[0766] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 764; SEQ ID NO: 766; and SEQ ID NO: 768 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 761 or the variable heavy chain sequence of SEQ ID NO: 762 or sequences that are at least 90% or 95% identical thereto.

[0767] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 784; SEQ ID NO: 786; and SEQ ID NO: 788 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 781 or the variable light chain sequence of SEQ ID NO: 782 or sequences that are at least 90% or 95% identical thereto.

[0768] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 763; SEQ ID NO: 765; SEQ ID NO: 767; and SEQ ID NO: 769 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 761 or the variable heavy chain sequence of SEQ ID NO: 762 or sequences that are at least 90% or 95% identical thereto.

[0769] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 783; SEQ ID NO: 785; SEQ ID NO: 787; and SEQ ID NO: 789 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 781 or the variable light chain sequence of SEQ ID NO: 782 or sequences that are at least 90% or 95% identical thereto.

[0770] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 762; the variable light chain region of SEQ ID NO: 782; the complementarity-determining regions (SEQ ID NO: 764; SEQ ID NO: 766; and SEQ ID NO: 768) of the variable heavy chain region of SEQ ID NO: 762; and the complementarity-determining regions (SEQ ID NO: 784; SEQ ID NO: 786; and SEQ ID NO: 788) of the variable light chain region of SEQ ID NO: 782 or sequences that are at least 90% or 95% identical thereto.

[0771] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 762; the variable light chain region of SEQ ID NO: 782; the framework regions (SEQ ID NO: 763; SEQ ID NO: 765; SEQ ID NO: 767; and SEQ ID NO: 769) of the variable heavy chain region of SEQ ID NO: 762; and the framework regions (SEQ ID NO: 783; SEQ ID NO: 785; SEQ ID NO: 787; and SEQ ID NO: 789) of the variable light chain region of SEQ ID NO: 782.

[0772] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab11.H, comprising, or alternatively consisting of, SEQ ID NO: 761 and SEQ ID NO: 781 or SEQ ID NO: 762 and SEQ ID NO: 782, or an antibody or antibody fragment comprising the CDRs of Ab11.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab11.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab11.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab11.H.

[0773] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab11.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 762 and the variable light chain sequence of SEQ ID NO: 782 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 762 and/or SEQ ID NO: 782 which retain the binding specificity for ACTH.

[0774] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab11.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab11.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0775] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab11.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0776] Antibody Ab11A.H

[0777] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth

below:

EVQLVESGGGLVQPGGSLRLSCAASGFTVSAYDILWVRQAPGKGLESIGMMYDDGDTYYAT
SAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS
SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 801).

[0778] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0779] EVQLVESGGGLVQPGGSLRLSCAASGFTVSAYDILWVRQAPGKGLESIGMMYDD
GDTYYATSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNIWGQGTLVTVSS
(SEQ ID NO: 802).

[0780] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab11A.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 810).

[0781] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSIGSSLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG
SGSGTEFTLTISSLQPDDFATYYCQSYEGSSSSYYGIGFGGGTKVEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 821).

[0782] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSIGSSLAWYQQKPGKAPKLLIYSASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYEGSSSSYYGIGFGGGTKVEIKR (SEQ ID NO: 822).

[0783] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab11A.H which contain a constant light chain sequence comprising the sequence set forth below: TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 830).

[0784] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 804; SEQ ID NO: 806; and SEQ ID NO: 808 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 801 or which contain the variable heavy chain sequence of SEQ ID NO: 802, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 824; SEQ ID NO: 826; and SEQ ID NO: 828 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 821 or which contain the variable light chain sequence of SEQ ID NO: 822, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0785] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 803; SEQ ID NO: 805; SEQ ID NO: 807; and SEQ ID NO: 809 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 801 or the variable heavy chain sequence of SEQ ID NO: 802, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 823; SEQ ID NO: 825; SEQ ID NO: 827; and SEQ ID NO: 829 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 821 or the variable light chain sequence of SEQ ID NO: 822, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0786] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0787] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 801 or SEQ ID NO: 802 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 821 or SEQ ID NO: 822 or polypeptides that are at least 90% or 95% identical thereto.

[0788] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 804; SEQ ID NO: 806; and SEQ ID NO: 808 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 801 or the variable heavy chain sequence of SEQ ID NO: 802 or sequences that are at least 90% or 95% identical thereto.

[0789] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 824; SEQ ID NO: 826; and SEQ ID NO: 828 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 821 or the variable light chain sequence of SEQ ID NO: 822 or sequences that are at least 90% or 95% identical thereto.

[0790] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 803; SEQ ID NO: 805; SEQ ID NO: 807; and SEQ ID NO: 809 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 801 or the variable heavy chain sequence of SEQ ID NO: 802 or sequences that are at least 90% or 95% identical thereto.

[0791] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 823; SEQ ID NO: 825; SEQ ID NO: 827; and SEQ ID NO: 829 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 821 or the variable light chain sequence of SEQ ID NO: 822 or sequences that are at least 90% or 95% identical thereto.

[0792] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 802; the variable light chain region of SEQ ID NO: 822; the complementarity-determining regions (SEQ ID NO: 804; SEQ ID NO: 806; and SEQ ID NO: 808) of the variable

heavy chain region of SEQ ID NO: 802; and the complementarity-determining regions (SEQ ID NO: 824; SEQ ID NO: 826; and SEQ ID NO: 828) of the variable light chain region of SEQ ID NO: 822 or sequences that are at least 90% or 95% identical thereto.

[0793] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 802; the variable light chain region of SEQ ID NO: 822; the framework regions (SEQ ID NO: 803; SEQ ID NO: 805; SEQ ID NO: 807; and SEQ ID NO: 809) of the variable heavy chain region of SEQ ID NO: 802; and the framework regions (SEQ ID NO: 823; SEQ ID NO: 825; SEQ ID NO: 827; and SEQ ID NO: 829) of the variable light chain region of SEQ ID NO: 822.

[0794] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab11A.H, comprising, or alternatively consisting of, SEQ ID NO: 801 and SEQ ID NO: 821 or SEQ ID NO: 802 and SEQ ID NO: 822, or an antibody or antibody fragment comprising the CDRs of Ab11A.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab11A.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab11A.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab11A.H.

[0795] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab11A.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 802 and the variable light chain sequence of SEQ ID NO: 822 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 802 and/or SEQ ID NO: 822 which retain the binding specificity for ACTH.

[0796] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab11A.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab11A.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0797] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab11A.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0798] Antibody Ab12.H

[0799] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAASGSSLSDYDMIWVRQAPGKGLESIGIIYDDGDTYYATS
AKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNMWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS
SSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 841).

[0800] In one embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable heavy chain sequence comprising the sequence set forth below:

[0801] EVQLVESGGGLVQPGGSLRLSCAASGSSLSDYDMIWVRQAPGKGLESIGIIYDDGD
TYYATSAKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVKGVSNMWGQGTLVTVSS (SEQ
ID NO: 842).

[0802] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that possess the same epitopic specificity as Ab12.H and which contain a constant heavy chain sequence comprising the polypeptide of SEQ ID NO: 886, 887, or 888 or comprising the sequence set forth below:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPGK (SEQ ID NO: 850).

[0803] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a light chain sequence comprising the sequence set forth below:

DIQMTQSPSTLSASVGDRVTITCQASQSIGSSLAWYQQKPGKAPKLLIYAASTLASGVPSRFSG
SGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSSYGVGFGGGTKVEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 861).

[0804] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain a variable light chain sequence comprising the sequence set forth below:
DIQMTQSPSTLSASVGDRVTITCQASQSIGSSLAWYQQKPGKAPKLLIYAASTLASGVPSRFSG SGSGTEFTLTISSLQPDDFATYYCQSYDGSSSSSYGVGFGGGTKVEIKR (SEQ ID NO: 862).

[0805] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that bind the same epitope as Ab12.H which contain a constant light chain sequence comprising the sequence set forth below:
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 870).

[0806] In another embodiment, the invention includes antibodies and antibody fragments having binding specificity to ACTH that contain one, two, or three of the polypeptide sequences of SEQ ID NO: 844; SEQ ID NO: 846; and SEQ ID NO: 848 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 841 or which contain the variable heavy chain sequence of SEQ ID NO: 842, and/or which further contain one, two, or three of the polypeptide sequences of SEQ ID NO: 864; SEQ ID NO: 866; and SEQ ID NO: 868 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 861 or which contain the variable light chain sequence of SEQ ID NO: 862, or antibodies or fragments containing combinations of sequences which are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical thereto. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the exemplified variable heavy chain and variable light chain sequences, or the heavy chain and light chain sequences set forth above, or sequences that are at least 90% or 95% identical thereto.

[0807] The invention further contemplates anti-ACTH antibodies and antibody fragments comprising one, two, three, or four of the polypeptide sequences of SEQ ID NO: 843; SEQ ID NO: 845; SEQ ID NO: 847; and SEQ ID NO: 849 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 841 or the variable heavy chain sequence of SEQ ID NO: 842, and/or one, two, three, or four of the polypeptide sequences of SEQ ID NO: 863; SEQ ID NO: 865; SEQ ID NO: 867; and SEQ ID NO: 869 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 861 or the variable light chain sequence of SEQ ID NO: 862, or combinations of these polypeptide sequences or sequences which are at least 80%, 90%, 95%, 96%, 97%, 98% or 99% identical therewith.

[0808] In another embodiment of the invention, the antibodies and antibody fragments of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and

light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0809] In another embodiment of the invention, the anti-ACTH antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 841 or SEQ ID NO: 842 or polypeptides that are at least 90% or 95% identical thereto. In another embodiment of the invention, the antibody or antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 861 or SEQ ID NO: 862 or polypeptides that are at least 90% or 95% identical thereto.

[0810] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 844; SEQ ID NO: 846; and SEQ ID NO: 848 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 841 or the variable heavy chain sequence of SEQ ID NO: 842 or sequences that are at least 90% or 95% identical thereto.

[0811] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, or three of the polypeptide sequences of SEQ ID NO: 864; SEQ ID NO: 866; and SEQ ID NO: 868 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain sequence of SEQ ID NO: 861 or the variable light chain sequence of SEQ ID NO: 862 or sequences that are at least 90% or 95% identical thereto.

[0812] In a further embodiment of the invention, the antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 843; SEQ ID NO: 845; SEQ ID NO: 847; and SEQ ID NO: 849 which correspond to the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 841 or the variable heavy chain sequence of SEQ ID NO: 842 or sequences that are at least 90% or 95% identical thereto.

[0813] In a further embodiment of the invention, the subject antibody or antibody fragment having binding specificity to ACTH comprises, or alternatively consists of, one, two, three, or four of the polypeptide sequences of SEQ ID NO: 863; SEQ ID NO: 865; SEQ ID NO: 867; and SEQ ID NO: 869 which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 861 or the variable light chain sequence of SEQ ID NO: 862 or sequences that are at least 90% or 95% identical thereto.

[0814] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, antibody or antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region

of SEQ ID NO: 842; the variable light chain region of SEQ ID NO: 862; the complementarity-determining regions (SEQ ID NO: 844; SEQ ID NO: 846; and SEQ ID NO: 848) of the variable heavy chain region of SEQ ID NO: 842; and the complementarity-determining regions (SEQ ID NO: 864; SEQ ID NO: 866; and SEQ ID NO: 868) of the variable light chain region of SEQ ID NO: 862 or sequences that are at least 90% or 95% identical thereto.

[0815] The invention also contemplates antibody or antibody fragments that include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable heavy chain region of SEQ ID NO: 842; the variable light chain region of SEQ ID NO: 862; the framework regions (SEQ ID NO: 843; SEQ ID NO: 845; SEQ ID NO: 847; and SEQ ID NO: 849) of the variable heavy chain region of SEQ ID NO: 842; and the framework regions (SEQ ID NO: 863; SEQ ID NO: 865; SEQ ID NO: 867; and SEQ ID NO: 869) of the variable light chain region of SEQ ID NO: 862.

[0816] In a particularly preferred embodiment of the invention, the anti-ACTH antibody is Ab12.H, comprising, or alternatively consisting of, SEQ ID NO: 841 and SEQ ID NO: 861 or SEQ ID NO: 842 and SEQ ID NO: 862, or an antibody or antibody fragment comprising the CDRs of Ab12.H and having at least one of the biological activities set forth herein or is an anti-ACTH antibody that competes with Ab12.H in binding ACTH, preferably one containing sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical to that of Ab12.H or an antibody that binds to the same or overlapping epitope(s) on ACTH as Ab12.H.

[0817] In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab12.H, the Fab fragment preferably includes the variable heavy chain sequence of SEQ ID NO: 842 and the variable light chain sequence of SEQ ID NO: 862 or sequences that are at least 90%, 95%, 96%, 97%, 98% or 99% identical thereto. This embodiment of the invention further includes Fabs containing additions, deletions, and variants of SEQ ID NO: 842 and/or SEQ ID NO: 862 which retain the binding specificity for ACTH.

[0818] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab12.H. In another embodiment of the invention, anti-ACTH antibodies such as Ab12.H or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example haploid or diploid yeast such as haploid or diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0819] In an additional embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH, including the heavy and/or light chains of Ab12.H as well as fragments, variants, combinations of one or more of the FRs, CDRs, the variable

heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them or sequences which are at least 90% or 95% identical thereto.

[0820] In another embodiment, the invention contemplates an isolated anti-ACTH antibody comprising a V_H polypeptide sequence selected from: SEQ ID NO:2, SEQ ID NO: 42, SEQ ID NO: 82, SEQ ID NO: 122, SEQ ID NO: 162, SEQ ID NO: 202, SEQ ID NO: 242, SEQ ID NO: 282, SEQ ID NO: 322, SEQ ID NO: 362, SEQ ID NO: 402, SEQ ID NO: 442, SEQ ID NO: 482, SEQ ID NO: 522, SEQ ID NO: 562, SEQ ID NO: 602, SEQ ID NO: 642, SEQ ID NO: 682, SEQ ID NO: 722, SEQ ID NO: 762, SEQ ID NO: 802, SEQ ID NO: 842, or a variant thereof; and further comprising a V_L polypeptide sequence selected from: SEQ ID NO: 22, SEQ ID NO: 62, SEQ ID NO: 102, SEQ ID NO: 142, SEQ ID NO: 182, SEQ ID NO: 222, SEQ ID NO: 262, SEQ ID NO: 302, SEQ ID NO: 342, SEQ ID NO: 382, SEQ ID NO: 422, SEQ ID NO: 462, SEQ ID NO: 502, SEQ ID NO: 542, SEQ ID NO: 582, SEQ ID NO: 622, SEQ ID NO: 662, SEQ ID NO: 702, SEQ ID NO: 742, SEQ ID NO: 782, SEQ ID NO: 822, SEQ ID NO: 862,or a variant thereof, wherein one or more of the framework residues (FR residues) and/or CDR residues in said V_H or V_L polypeptide has been substituted with another amino acid residue resulting in an anti-ACTH antibody that specifically binds ACTH. The invention also includes humanized and chimeric forms of these antibodies. The chimeric and humanized antibodies may include an Fc derived from IgG1, IgG2, IgG3, or IgG4 constant regions.

[0821] In one embodiment of the invention, the chimeric or humanized antibodies or fragments or V_H or V_L polypeptides originate or are derived from one or more rabbit antibodies, e.g., a rabbit antibody isolated from a clonal rabbit B cell population.

[0822] In some aspects, the invention provides a vector comprising a nucleic acid molecule encoding an anti-ACTH antibody or fragment thereof as disclosed herein. In some embodiments, the invention provides a host cell comprising a nucleic acid molecule encoding an anti-ACTH antibody or fragment thereof as disclosed herein.

[0823] In some aspects, the invention provides an isolated antibody or antibody fragment that competes for binding to ACTH with an antibody or antibody fragment disclosed herein.

[0824] In some aspects, the invention provides a nucleic acid molecule encoding an antibody or antibody fragment as disclosed herein.

[0825] In some aspects, the invention provides a pharmaceutical or diagnostic composition comprising at least one antibody or antibody fragment as disclosed herein.

[0826] In some aspects, the invention provides a method for treating or preventing a condition associated with elevated plasma cortisol, corticosterone, and/or aldosterone levels in a subject, comprising administering to a subject in need thereof an effective amount of at least one isolated antibody or antibody fragment as disclosed herein. The anti-ACTH antibody may reduce plasma cortisol levels. In embodiments, the anti-ACTH antibody may reduce plasma cortisol levels and/or

may not abolish plasma cortisol levels. In embodiments, the anti-ACTH antibody may reduce plasma corticosterone levels, but may not abolish plasma corticosterone levels.

[0827] In some aspects, the invention provides a method of inhibiting binding of ACTH to MCR (e.g., MC2R) in a subject comprising administering an effective amount of at least one antibody or antibody fragment as disclosed herein.

[0828] In some aspects, the invention provides an antibody or antibody fragment that selectively binds to ACTH, wherein the antibody or antibody fragment binds to ACTH with a K_D of less than or equal to $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M; preferably, with a K_D of less than or equal to $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M; more preferably, with a K_D that is less than about 100 nM, less than about 50 pM, less than about 40 pM, less than about 25 pM, less than about 1 pM, between about 10 pM and about 100 pM, between about 1 pM and about 100 pM, or between about 1 pM and about 10 pM.

[0829] The inventive antibodies and fragments thereof may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

[0830] Antibodies or fragments thereof may also be chemically modified to provide additional advantages such as increased solubility, stability and circulating time (*in vivo* half-life) of the polypeptide, or decreased immunogenicity (See U.S. Pat. No. 4,179,337). The chemical moieties for derivatization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The antibodies and fragments thereof may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0831] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000,

16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa. Branched polyethylene glycols are described, for example, in U.S. Pat. No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0832] There are a number of attachment methods available to those skilled in the art, *See* e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), *See also* Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0833] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to polypeptides via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof).

[0834] Alternatively, antibodies or fragments thereof may have increased *in vivo* half-lives via fusion with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (*See*, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)) or other circulating blood proteins such as transferrin or ferritin. In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1-585 of human serum albumin as shown in FIGS. 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[0835] Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, *beta*-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein,

fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin, and dansyl chloride. Further exemplary chemiluminescent moieties include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and aequorin. Further exemplary radioactive materials include, but are not limited to, Iodine 125 (^{125}I), Carbon 14 (^{14}C), Sulfur 35 (^{35}S), Tritium (^{3}H) and Phosphorus 32 (^{32}P).

[0836] Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclothosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimitotic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (Taxol), ricin, pseudomonas exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, teniposide, colchicine, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mitotane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

[0837] Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine and bleomycin. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and *Pseudomonas* toxin may be conjugated to the humanized or chimeric antibodies, or binding fragments thereof (Youle, et al., *PNAS USA* 77:5483 (1980); Gilliland, et al., *PNAS USA* 77:4539 (1980); Krolick, et al., *PNAS USA* 77:5419 (1980)).

[0838] Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32 (^{32}P), Scandium-47 (^{47}Sc), Copper-67 (^{67}Cu), Gallium-67 (^{67}Ga), Yttrium-88 (^{88}Y), Yttrium-90 (^{90}Y), Iodine-125 (^{125}I), Iodine-131 (^{131}I), Samarium-153 (^{153}Sm), Lutetium-177 (^{177}Lu), Rhenium-186 (^{186}Re) or Rhenium-188 (^{188}Re), and alpha-emitters such as Astatine-211 (^{211}At), Lead-212 (^{212}Pb), Bismuth-212 (^{212}Bi) or -213 (^{213}Bi) or Actinium-225 (^{225}Ac).

[0839] Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those methods described by Hunter *et al*, *Nature*

144:945 (1962); David *et al*, *Biochemistry* 13:1014 (1974); Pain *et al*, *J. Immunol. Meth.* 40:219 (1981); and Nygren, J., *Histochem. and Cytochem.* 30:407 (1982).

[0840] Embodiments described herein further include variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camelbodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth herein. These may contain, e.g., conservative substitution mutations, (i.e., the substitution of one or more amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, e.g., one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art.

[0841] In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

[0842] In another embodiment, the invention further contemplates the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-ACTH activity. Non-limiting examples of anti-ACTH activity are set forth herein.

[0843] In another embodiment, the invention further contemplates the generation and use of antibodies that bind any of the foregoing sequences, including, but not limited to, anti-idiotypic antibodies. In an exemplary embodiment, such an anti-idiotypic antibody could be administered to a subject who has received an anti-ACTH antibody to modulate, reduce, or neutralize, the effect of the anti-ACTH antibody. Such antibodies could also be useful for treatment of an autoimmune disease characterized by the presence of anti-ACTH antibodies. A further exemplary use of such antibodies, e.g., anti-idiotypic antibodies, is for detection of the anti-ACTH antibodies of the present invention, for example to monitor the levels of the anti-ACTH antibodies present in a subject's blood or other bodily fluids. For example, in one embodiment, the invention provides a method of using the anti-idiotypic antibody to monitor the *in vivo* levels of said anti-ACTH antibody or antibody fragment in a subject or to neutralize said anti-ACTH antibody in a subject being administered said anti-ACTH antibody or antibody fragment.

[0844] The present invention also contemplates anti-ACTH antibodies comprising any of the polypeptide or polynucleotide sequences described herein substituted for any of the other polynucleotide sequences described herein. For example, without limitation thereto, the present

invention contemplates antibodies comprising the combination of any of the variable light chain and variable heavy chain sequences described herein, and further contemplates antibodies resulting from substitution of any of the CDR sequences described herein for any of the other CDR sequences described herein.

[0845] ***Polynucleotides Encoding Anti-ACTH Antibody Polypeptides***

[0846] The invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH.

[0847] Antibody Ab1

[0848] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 1: cagtcagtgaaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtaactatgac atgatctgggtccgccaggctccagggaaggggctggaatccatcgggatgatttatgatgatggtgacacatactacgcgagttgggcgaaagg ccgattcaccatctccaaaacctcgaccacggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtg agtaatcactggggcccaggcaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcac ctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcgg cgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagaccta catctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcc cagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcg tggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggg aggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctc caacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccg ggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggca gccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggc agcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 11).

[0849] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 2: cagtcagtgaaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtaactatgac atgatctgggtccgccaggctccagggaaggggctggaatccatcgggatgatttatgatgatggtgacacatactacgcgagttgggcgaaagg ccgattcaccatctccaaaacctcgaccacggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtg agtaatcactggggcccaggcaccctcgtcaccgtctcgagc (SEQ ID NO: 12).

[0850] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain

polypeptide sequence of SEQ ID NO: 10: gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 20).

[0851] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 21: gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtagtta cttagcctggtatcagcagaaaccagggcagcctcccaaactcctgatctactctgcatccactctggcatctggggtcccatcgcggttcaaaggc aggggatctgggacagaattcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtggta gtagttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagca gttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgg gtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgag aaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 31).

[0852] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 22: gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtagtta cttagcctggtatcagcagaaaccagggcagcctcccaaactcctgatctactctgcatccactctggcatctggggtcccatcgcggttcaaaggc aggggatctgggacagaattcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtggta gtagttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 32).

[0853] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 30: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc

tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 40).

[0854] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 14; SEQ ID NO: 16; and SEQ ID NO: 18, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 1 or the variable heavy chain sequence of SEQ ID NO: 2, and/or one or more of the polynucleotide sequences of SEQ ID NO: 34; SEQ ID NO: 36 and SEQ ID NO: 38, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 21 or the variable light chain sequence of SEQ ID NO: 22, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0855] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 13; SEQ ID NO: 15; SEQ ID NO: 17; and SEQ ID NO: 19, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 1 or the variable heavy chain sequence of SEQ ID NO: 2, and/or one or more of the polynucleotide sequences of SEQ ID NO: 33; SEQ ID NO: 35; SEQ ID NO: 37; and SEQ ID NO: 39, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 21 or the variable light chain sequence of SEQ ID NO: 22, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0856] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 11 encoding the heavy chain sequence of SEQ ID NO: 1; the polynucleotide SEQ ID NO: 12 encoding the variable heavy chain sequence of SEQ ID NO: 2; the polynucleotide SEQ ID NO: 31 encoding the light chain sequence of SEQ ID NO: 21; the polynucleotide SEQ ID NO: 32 encoding the variable light chain

sequence of SEQ ID NO: 22; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 14; SEQ ID NO: 16; and SEQ ID NO: 18) of the heavy chain sequence of SEQ ID NO: 1 or the variable heavy chain sequence of SEQ ID NO: 2; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 34; SEQ ID NO: 36; and SEQ ID NO: 38) of the light chain sequence of SEQ ID NO: 21 or the variable light chain sequence of SEQ ID NO: 22; polynucleotides encoding the framework regions (SEQ ID NO: 13; SEQ ID NO: 15; SEQ ID NO: 17; and SEQ ID NO: 19) of the heavy chain sequence of SEQ ID NO: 1 or the variable heavy chain sequence of SEQ ID NO: 2; and polynucleotides encoding the framework regions (SEQ ID NO: 33; SEQ ID NO: 35; SEQ ID NO: 37; and SEQ ID NO: 39) of the light chain sequence of SEQ ID NO: 21 or the variable light chain sequence of SEQ ID NO: 22.

[0857] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab1, the polynucleotides encoding the full length Ab1 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 11 encoding the heavy chain sequence of SEQ ID NO: 1 and the polynucleotide SEQ ID NO: 31 encoding the light chain sequence of SEQ ID NO: 21.

[0858] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab1 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab1 or Fab fragments thereof may be produced via expression of Ab1 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0859] Antibody Ab2

[0860] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 41:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtaagtatgac
atgatctgggtccgccaggctccagggaaggggctggaatccatcgggatcatttatgatgatggcgacacatattacgcgagttgggcgaaagg
ccgattcaccatctcccaaacctcgaccacggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtg
agtaatatctggggccaaggcaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccccctggcaccctcctccaagagcac
ctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcgg

cgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagaccta catctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcc cagcacctgaactcctgggggggaccgtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcg tggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggg aggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctc caacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccg ggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggca gccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggc agcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 51).

[0861] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 42: cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtaagtatgac atgatctgggtccgccaggctccagggaaggggctggaatccatcgggatcatttatgatgatggcgacacatattacgcgagttgggcgaaagg ccgattcaccatctcccaaacctcgaccacggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtg agtaatatctggggccaaggcaccctcgtcaccgtctcgagc (SEQ ID NO: 52).

[0862] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 50: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 60).

[0863] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 61: gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtaacta cttagcctggtatcagcagaaaacagggcagcctcccaagctcctgatctactctgcatccactctggcatctggggtcccatcgcggttcaaaggc

agtggatctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgagggtagtagtagta gtagttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagca gttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgg gtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgag aaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 71).

[0864] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 62: gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtaacta cttagcctggtatcagcagaaaacagggcagcctcccaagctcctgatctactctgcatccactctggcatctggggtcccatcgcggttcaaaggc agtggatctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgagggtagtagtagta gtagttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 72).

[0865] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 70: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 80).

[0866] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 54; SEQ ID NO: 56; and SEQ ID NO: 58, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 41 or the variable heavy chain sequence of SEQ ID NO: 42, and/or one or more of the polynucleotide sequences of SEQ ID NO: 74; SEQ ID NO: 76 and SEQ ID NO: 78, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 61 or the variable light chain sequence of SEQ ID NO: 62, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0867] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 53; SEQ ID NO: 55; SEQ ID NO: 57; and SEQ ID NO: 59,

which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 41 or the variable heavy chain sequence of SEQ ID NO: 42, and/or one or more of the polynucleotide sequences of SEQ ID NO: 73; SEQ ID NO: 75; SEQ ID NO: 77; and SEQ ID NO: 79, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 61 or the variable light chain sequence of SEQ ID NO: 62, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0868] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 51 encoding the heavy chain sequence of SEQ ID NO: 41; the polynucleotide SEQ ID NO: 52 encoding the variable heavy chain sequence of SEQ ID NO: 42; the polynucleotide SEQ ID NO: 71 encoding the light chain sequence of SEQ ID NO: 61; the polynucleotide SEQ ID NO: 72 encoding the variable light chain sequence of SEQ ID NO: 62; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 54; SEQ ID NO: 56; and SEQ ID NO: 58) of the heavy chain sequence of SEQ ID NO: 41 or the variable heavy chain sequence of SEQ ID NO: 42; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 74; SEQ ID NO: 76; and SEQ ID NO: 78) of the light chain sequence of SEQ ID NO: 61 or the variable light chain sequence of SEQ ID NO: 62; polynucleotides encoding the framework regions (SEQ ID NO: 53; SEQ ID NO: 55; SEQ ID NO: 57; and SEQ ID NO: 59) of the heavy chain sequence of SEQ ID NO: 41 or the variable heavy chain sequence of SEQ ID NO: 42; and polynucleotides encoding the framework regions (SEQ ID NO: 73; SEQ ID NO: 75; SEQ ID NO: 77; and SEQ ID NO: 79) of the light chain sequence of SEQ ID NO: 61 or the variable light chain sequence of SEQ ID NO: 62.

[0869] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab2, the polynucleotides encoding the full length Ab2 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 51 encoding the heavy chain sequence of SEQ ID NO: 41 and the polynucleotide SEQ ID NO: 71 encoding the light chain sequence of SEQ ID NO: 61.

[0870] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in

fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab2 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab2 or Fab fragments thereof may be produced via expression of Ab2 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0871] Antibody Ab3

[0872] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 81: cagtcgctggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggatcctccctcagtaattttgaca tgatctgggtccgccaggctccagggaaggggctggaatccatcgggatcatttatgattttggtagcacatactacgcgagctgggcgaaaggcc gcttcaccatctccagaacctcgtcgaccacggtggatctgaaaatcatcagtccgacaattgaggacacggccacctatttctgtgtcaaaggtgtg agtaatatctggggccaaggcaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcac ctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcgg cgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagaccta catctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcc cagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccctgaggtcacatgcg tggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggg aggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctc caacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccg ggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggca gccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggc agcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 91).

[0873] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 82: cagtcgctggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggatcctccctcagtaattttgaca tgatctgggtccgccaggctccagggaaggggctggaatccatcgggatcatttatgattttggtagcacatactacgcgagctgggcgaaaggcc gcttcaccatctccagaacctcgtcgaccacggtggatctgaaaatcatcagtccgacaattgaggacacggccacctatttctgtgtcaaaggtgtg agtaatatctggggccaaggcaccctcgtcaccgtctcgagc (SEQ ID NO: 92).

[0874] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 90:
gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact
acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact
ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga
cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc
cccaaaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc
accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca
aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg
gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact
ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 100).

[0875] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 101:
gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtgaggatattagtagtaat
ttagcctggtatcagcagaaattagggcagcctcccaagctcctgatctactctgcatccactctggcatctggggtcccatcgcggttcaaaggcag
tggatctgggacagagttcactctcgccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagtagta
gttatggtattggtttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttg
aaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggta
actcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaa
cacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 111).

[0876] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 102:
gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtgaggatattagtagtaat
ttagcctggtatcagcagaaattagggcagcctcccaagctcctgatctactctgcatccactctggcatctggggtcccatcgcggttcaaaggcag
tggatctgggacagagttcactctcgccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagtagta
gttatggtattggtttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 112).

[0877] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 110:
acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca

gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 120).

[0878] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 94; SEQ ID NO: 96; and SEQ ID NO: 98, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 81 or the variable heavy chain sequence of SEQ ID NO: 82, and/or one or more of the polynucleotide sequences of SEQ ID NO: 114; SEQ ID NO: 116 and SEQ ID NO: 118, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 101 or the variable light chain sequence of SEQ ID NO: 102, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0879] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 93; SEQ ID NO: 95; SEQ ID NO: 97; and SEQ ID NO: 99, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 81 or the variable heavy chain sequence of SEQ ID NO: 82, and/or one or more of the polynucleotide sequences of SEQ ID NO: 113; SEQ ID NO: 115; SEQ ID NO: 117; and SEQ ID NO: 119, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 101 or the variable light chain sequence of SEQ ID NO: 102, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0880] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 91 encoding the heavy chain sequence of SEQ ID NO: 81; the polynucleotide SEQ ID NO: 92 encoding the variable heavy chain sequence of SEQ ID NO: 82; the polynucleotide SEQ ID NO: 111 encoding the light chain

sequence of SEQ ID NO: 101; the polynucleotide SEQ ID NO: 112 encoding the variable light chain sequence of SEQ ID NO: 102; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 94; SEQ ID NO: 96; and SEQ ID NO: 98) of the heavy chain sequence of SEQ ID NO: 81 or the variable heavy chain sequence of SEQ ID NO: 82; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 114; SEQ ID NO: 116; and SEQ ID NO: 118) of the light chain sequence of SEQ ID NO: 101 or the variable light chain sequence of SEQ ID NO: 102; polynucleotides encoding the framework regions (SEQ ID NO: 93; SEQ ID NO: 95; SEQ ID NO: 97; and SEQ ID NO: 99) of the heavy chain sequence of SEQ ID NO: 81 or the variable heavy chain sequence of SEQ ID NO: 82; and polynucleotides encoding the framework regions (SEQ ID NO: 113; SEQ ID NO: 115; SEQ ID NO: 117; and SEQ ID NO: 119) of the light chain sequence of SEQ ID NO: 101 or the variable light chain sequence of SEQ ID NO: 102.

[0881] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab3, the polynucleotides encoding the full length Ab3 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 91 encoding the heavy chain sequence of SEQ ID NO: 81 and the polynucleotide SEQ ID NO: 111 encoding the light chain sequence of SEQ ID NO: 101.

[0882] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab3 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab3 or Fab fragments thereof may be produced via expression of Ab3 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0883] Antibody Ab4

[0884] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 121:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctacacagtctctggattctccctcagtaagcatgac
atgatctgggtccgccaggctccagggaaggggctggaatccatcgggatcatttatgatgatggtgatacatactacgcgaattgggcgaaaggc
cgattcaccatctccaaaacctcgaccacggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtga
gtaatatctggggcccaggcaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccccctggcaccctcctccaagagcacct

ctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcg tgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacat ctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgccca gcacctgaactcctgggggggaccgtcagtcttcctcttccccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtg gtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgcgggag gagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctcca acaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccggg aggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagc cggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcag caggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 131).

[0885] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 122: cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctacacagtctctggattctccctcagtaagcatgac atgatctgggtccgccaggctccagggaaggggctggaatccatcgggatcatttatgatgatggtgatacatactacgcgaattgggcgaaaggc cgattcaccatctccaaaacctcgaccacggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtga gtaatatctggggcccaggcaccctcgtcaccgtctcgagc (SEQ ID NO: 132).

[0886] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 130: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 140).

[0887] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 141: gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccgggccagtcagagcattagtgtcta

cctcgcctggtatcagcagaaagcagggcagcctcccaagctcctgatctaccaggcatccaaactggcctctggggtcccatcgcggttcaaag gcagtggatctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagt agtagttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagca gttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgg gtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgag aaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 151).

[0888] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 142: gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccgggccagtcagagcattagtgtcta cctcgcctggtatcagcagaaagcagggcagcctcccaagctcctgatctaccaggcatccaaactggcctctggggtcccatcgcggttcaaag gcagtggatctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagt agtagttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 152).

[0889] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 150: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 160).

[0890] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 134; SEQ ID NO: 136; and SEQ ID NO: 138, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 121 or the variable heavy chain sequence of SEQ ID NO: 122, and/or one or more of the polynucleotide sequences of SEQ ID NO: 154; SEQ ID NO: 156 and SEQ ID NO: 158, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 141 or the variable light chain sequence of SEQ ID NO: 142, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0891] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the

polynucleotide sequences of SEQ ID NO: 133; SEQ ID NO: 135; SEQ ID NO: 137; and SEQ ID NO: 139, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 121 or the variable heavy chain sequence of SEQ ID NO: 122, and/or one or more of the polynucleotide sequences of SEQ ID NO: 153; SEQ ID NO: 155; SEQ ID NO: 157; and SEQ ID NO: 159, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 141 or the variable light chain sequence of SEQ ID NO: 142, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0892] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 131 encoding the heavy chain sequence of SEQ ID NO: 121; the polynucleotide SEQ ID NO: 132 encoding the variable heavy chain sequence of SEQ ID NO: 122; the polynucleotide SEQ ID NO: 151 encoding the light chain sequence of SEQ ID NO: 141; the polynucleotide SEQ ID NO: 152 encoding the variable light chain sequence of SEQ ID NO: 142; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 134; SEQ ID NO: 136; and SEQ ID NO: 138) of the heavy chain sequence of SEQ ID NO: 121 or the variable heavy chain sequence of SEQ ID NO: 122; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 154; SEQ ID NO: 156; and SEQ ID NO: 158) of the light chain sequence of SEQ ID NO: 141 or the variable light chain sequence of SEQ ID NO: 142; polynucleotides encoding the framework regions (SEQ ID NO: 133; SEQ ID NO: 135; SEQ ID NO: 137; and SEQ ID NO: 139) of the heavy chain sequence of SEQ ID NO: 121 or the variable heavy chain sequence of SEQ ID NO: 122; and polynucleotides encoding the framework regions (SEQ ID NO: 153; SEQ ID NO: 155; SEQ ID NO: 157; and SEQ ID NO: 159) of the light chain sequence of SEQ ID NO: 141 or the variable light chain sequence of SEQ ID NO: 142.

[0893] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab4, the polynucleotides encoding the full length Ab4 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 131 encoding the heavy chain sequence of SEQ ID NO: 121 and the polynucleotide SEQ ID NO: 151 encoding the light chain sequence of SEQ ID NO: 141.

[0894] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab4 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab4 or Fab fragments thereof may be produced via expression of Ab4 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0895] Antibody Ab5

[0896] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 161:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtagctatgca
atgagctgggtccgccaggctccaggggaggggctggaatggatcggaatcattagtgatagtggtagcacatactacgcgagctgggcgaaag
gccgattcaccatctccaaaacctcgaccacggtggatctgaaaatcaccagtccgacaaccgaggacacggccacctatttctgtgccagagag
cccgagtacggctacgatgactatggtgattgggtttctgacttatggggccagggcaccctggtcaccgtctcgagcgcctccaccaagggccca
tcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgac
ggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgac
cgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaa
tcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacacc
ctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgt
ggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactg
gctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccg
agaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagc
gacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctcta
cagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcag
aagagcctctccctgtctccgggtaaa (SEQ ID NO: 171).

[0897] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 162:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtagctatgca
atgagctgggtccgccaggctccaggggaggggctggaatggatcggaatcattagtgatagtggtagcacatactacgcgagctgggcgaaag

gccgattcaccatctccaaaacctcgaccacggtggatctgaaaatcaccagtccgacaaccgaggacacggccacctatttctgtgccagagag cccgagtacggctacgatgactatggtgattgggtttctgacttatggggccagggcaccctggtcaccgtctcgagc (SEQ ID NO: 172).

[0898] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 170: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 180).

[0899] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 181: gctgacattgtgatgacccagactccagcctccgtgtctgaacctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtagtt acttatcctggtatcagcagaaaccagggcagcctcccaagctcctgatctacagggcatccactctggcatctggggtcccatcgcggttcaaag gcagtggatctgggacacagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctattattatagtagtagtat tacttatcgtaatgctttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagtt gaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggt aactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaa acacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 191).

[0900] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 182: gctgacattgtgatgacccagactccagcctccgtgtctgaacctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtagtt acttatcctggtatcagcagaaaccagggcagcctcccaagctcctgatctacagggcatccactctggcatctggggtcccatcgcggttcaaag gcagtggatctgggacacagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctattattatagtagtagtat tacttatcgtaatgctttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 192).

[0901] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain

polypeptide sequence of SEQ ID NO: 190: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 200).

[0902] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 174; SEQ ID NO: 176; and SEQ ID NO: 178, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 161 or the variable heavy chain sequence of SEQ ID NO: 162, and/or one or more of the polynucleotide sequences of SEQ ID NO: 194; SEQ ID NO: 196 and SEQ ID NO: 198, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 181 or the variable light chain sequence of SEQ ID NO: 182, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0903] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 173; SEQ ID NO: 175; SEQ ID NO: 177; and SEQ ID NO: 179, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 161 or the variable heavy chain sequence of SEQ ID NO: 162, and/or one or more of the polynucleotide sequences of SEQ ID NO: 193; SEQ ID NO: 195; SEQ ID NO: 197; and SEQ ID NO: 199, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 181 or the variable light chain sequence of SEQ ID NO: 182, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0904] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 171 encoding the

heavy chain sequence of SEQ ID NO: 161; the polynucleotide SEQ ID NO: 172 encoding the variable heavy chain sequence of SEQ ID NO: 162; the polynucleotide SEQ ID NO: 191 encoding the light chain sequence of SEQ ID NO: 181; the polynucleotide SEQ ID NO: 192 encoding the variable light chain sequence of SEQ ID NO: 182; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 174; SEQ ID NO: 176; and SEQ ID NO: 178) of the heavy chain sequence of SEQ ID NO: 161 or the variable heavy chain sequence of SEQ ID NO: 162; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 194; SEQ ID NO: 196; and SEQ ID NO: 198) of the light chain sequence of SEQ ID NO: 181 or the variable light chain sequence of SEQ ID NO: 182; polynucleotides encoding the framework regions (SEQ ID NO: 173; SEQ ID NO: 175; SEQ ID NO: 177; and SEQ ID NO: 179) of the heavy chain sequence of SEQ ID NO: 161 or the variable heavy chain sequence of SEQ ID NO: 162; and polynucleotides encoding the framework regions (SEQ ID NO: 193; SEQ ID NO: 195; SEQ ID NO: 197; and SEQ ID NO: 199) of the light chain sequence of SEQ ID NO: 181 or the variable light chain sequence of SEQ ID NO: 182.

[0905] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab5, the polynucleotides encoding the full length Ab5 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 171 encoding the heavy chain sequence of SEQ ID NO: 161 and the polynucleotide SEQ ID NO: 191 encoding the light chain sequence of SEQ ID NO: 181.

[0906] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab5 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab5 or Fab fragments thereof may be produced via expression of Ab5 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0907] Antibody Ab6

[0908] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 201:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcactgactatgca
atgagctgggtccgccaggctccaggggaggggctggaatggatcggaatcattagtgatagtggtagcacatactacgcgagctgggcgaaag

gccgattcaccttctccaaaacctcgaccacggtggatctgagaatcaccagtccgaccaccgaggacacggccacctatttctgtgccagagagc
ccgagtacggctacgatgagtatggtgattgggtttctgacttatggggcccaggcaccctcgtcaccgtctcgagcgcctccaccaagggcccat
cggtcttccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacg
gtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgacc
gtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaat
cttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggacgtcagtcttcctcttcccccaaaacccaaggacaccc
tcatgatctcccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtg
gaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactgg
ctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccga
gaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcg
acatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctac
agcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcaga
agagcctctccctgtctccgggtaaa (SEQ ID NO: 211).

[0909] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 202:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacaccccctgacactcacctgcacagtctctggattctccctcactgactatgca
atgagctgggtccgccaggctccaggggaggggctggaatggatcggaatcattagtgatagtggtagcacatactacgcgagctgggcgaaag
gccgattcaccttctccaaaacctcgaccacggtggatctgagaatcaccagtccgaccaccgaggacacggccacctatttctgtgccagagagc
ccgagtacggctacgatgagtatggtgattgggtttctgacttatggggcccaggcaccctcgtcaccgtctcgagc (SEQ ID NO: 212).

[0910] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 210:
gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact
acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact
ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga
cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggacgtcagtcttcctcttccc
cccaaaacccaaggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc
accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctcca
aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg
gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact
ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 220).

[0911] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide

sequence of SEQ ID NO: 221: gctgacattgtgatgacccagactccagcctccgtggaggcagctgtgggaggcgcagtcaccatcaagtgccaggccactcagagcattggtaa taatttagcctggtatcagcagaaaccagggcagcctcccaagctcctgatctacagggcatccactctggcatctggggtcccatcgcggttcaaa ggcagtgggtctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctattattatagtagtagt attacttatcataatgctttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagca gttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgg gtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgag aaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 231).

[0912] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 222: gctgacattgtgatgacccagactccagcctccgtggaggcagctgtgggaggcgcagtcaccatcaagtgccaggccactcagagcattggtaa taatttagcctggtatcagcagaaaccagggcagcctcccaagctcctgatctacagggcatccactctggcatctggggtcccatcgcggttcaaa ggcagtgggtctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctattattatagtagtagt attacttatcataatgctttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 232).

[0913] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 230: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 240).

[0914] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 201 or the variable heavy chain sequence of SEQ ID NO: 202, and/or one or more of the polynucleotide sequences of SEQ ID NO: 234; SEQ ID NO: 236 and SEQ ID NO: 238, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 221 or the variable light chain sequence of SEQ ID NO: 222, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0915] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 213; SEQ ID NO: 215; SEQ ID NO: 217; and SEQ ID NO: 219, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 201 or the variable heavy chain sequence of SEQ ID NO: 202, and/or one or more of the polynucleotide sequences of SEQ ID NO: 233; SEQ ID NO: 235; SEQ ID NO: 237; and SEQ ID NO: 239, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 221 or the variable light chain sequence of SEQ ID NO: 222, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0916] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201; the polynucleotide SEQ ID NO: 212 encoding the variable heavy chain sequence of SEQ ID NO: 202; the polynucleotide SEQ ID NO: 231 encoding the light chain sequence of SEQ ID NO: 221; the polynucleotide SEQ ID NO: 232 encoding the variable light chain sequence of SEQ ID NO: 222; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218) of the heavy chain sequence of SEQ ID NO: 201 or the variable heavy chain sequence of SEQ ID NO: 202; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238) of the light chain sequence of SEQ ID NO: 221 or the variable light chain sequence of SEQ ID NO: 222; polynucleotides encoding the framework regions (SEQ ID NO: 213; SEQ ID NO: 215; SEQ ID NO: 217; and SEQ ID NO: 219) of the heavy chain sequence of SEQ ID NO: 201 or the variable heavy chain sequence of SEQ ID NO: 202; and polynucleotides encoding the framework regions (SEQ ID NO: 233; SEQ ID NO: 235; SEQ ID NO: 237; and SEQ ID NO: 239) of the light chain sequence of SEQ ID NO: 221 or the variable light chain sequence of SEQ ID NO: 222.

[0917] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab6, the polynucleotides encoding the full length Ab6 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 211

encoding the heavy chain sequence of SEQ ID NO: 201 and the polynucleotide SEQ ID NO: 231 encoding the light chain sequence of SEQ ID NO: 221.

[0918] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab6 or Fab fragments thereof may be produced via expression of Ab6 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0919] Antibody Ab7

[0920] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 241:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtagctatgca
atgagctgggtccgccaggctccaggggaggggctggaatggatcggaatcattagtgatagtggtagcacatactacgcgagctgggcgaaag
gccgattcaccatctccaaaacctcgaccacggtggatctgagaatcaccagtccgacaaccgaggacacggccacctatttctgtgccagagag
cccgagtacggctacgatgactatggtgattgggtttctgacttatggggccaaggcaccctcgtcaccgtctcgagcgcctccaccaagggccca
tcggtcttcccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgac
ggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgac
cgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaa
tcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacacc
ctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgt
ggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactg
gctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccg
agaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagc
gacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctcta
cagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcag
aagagcctctccctgtctccgggtaaa (SEQ ID NO: 251).

[0921] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 242:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtagctatgca

atgagctgggtccgccaggctccaggggaggggctggaatggatcggaatcattagtgatagtggtagcacatactacgcgagctgggcgaaag gccgattcaccatctccaaaacctcgaccacggtggatctgagaatcaccagtccgacaaccgaggacacggccacctatttctgtgccagagag cccgagtacggctacgatgactatggtgattgggtttctgacttatggggccaaggcaccctcgtcaccgtctcgagc (SEQ ID NO: 252).

[0922] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 250: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 260).

[0923] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 261: gctgacattgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtga ttacttatcctggtatcagcagaaaccagggcagcctcccaagctcctgatctacagggcatccactctggcatctggggtcccatcgcggttcaaa ggcagtggatctgggacacagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctattattatagtagtagt attacttatcgtaatgctttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagca gttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgg gtaactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgag aaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 271).

[0924] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 262: gctgacattgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtga ttacttatcctggtatcagcagaaaccagggcagcctcccaagctcctgatctacagggcatccactctggcatctggggtcccatcgcggttcaaa ggcagtggatctgggacacagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctattattatagtagtagt attacttatcgtaatgctttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 272).

[0925] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 270: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 280).

[0926] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 254; SEQ ID NO: 256; and SEQ ID NO: 258, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 241 or the variable heavy chain sequence of SEQ ID NO: 242, and/or one or more of the polynucleotide sequences of SEQ ID NO: 274; SEQ ID NO: 276 and SEQ ID NO: 278, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 261 or the variable light chain sequence of SEQ ID NO: 262, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0927] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 253; SEQ ID NO: 255; SEQ ID NO: 257; and SEQ ID NO: 259, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 241 or the variable heavy chain sequence of SEQ ID NO: 242, and/or one or more of the polynucleotide sequences of SEQ ID NO: 273; SEQ ID NO: 275; SEQ ID NO: 277; and SEQ ID NO: 279, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 261 or the variable light chain sequence of SEQ ID NO: 262, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0928] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH

comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 251 encoding the heavy chain sequence of SEQ ID NO: 241; the polynucleotide SEQ ID NO: 252 encoding the variable heavy chain sequence of SEQ ID NO: 242; the polynucleotide SEQ ID NO: 271 encoding the light chain sequence of SEQ ID NO: 261; the polynucleotide SEQ ID NO: 272 encoding the variable light chain sequence of SEQ ID NO: 262; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 254; SEQ ID NO: 256; and SEQ ID NO: 258) of the heavy chain sequence of SEQ ID NO: 241 or the variable heavy chain sequence of SEQ ID NO: 242; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 274; SEQ ID NO: 276; and SEQ ID NO: 278) of the light chain sequence of SEQ ID NO: 261 or the variable light chain sequence of SEQ ID NO: 262; polynucleotides encoding the framework regions (SEQ ID NO: 253; SEQ ID NO: 255; SEQ ID NO: 257; and SEQ ID NO: 259) of the heavy chain sequence of SEQ ID NO: 241 or the variable heavy chain sequence of SEQ ID NO: 242; and polynucleotides encoding the framework regions (SEQ ID NO: 273; SEQ ID NO: 275; SEQ ID NO: 277; and SEQ ID NO: 279) of the light chain sequence of SEQ ID NO: 261 or the variable light chain sequence of SEQ ID NO: 262.

[0929] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab7, the polynucleotides encoding the full length Ab7 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 251 encoding the heavy chain sequence of SEQ ID NO: 241 and the polynucleotide SEQ ID NO: 271 encoding the light chain sequence of SEQ ID NO: 261.

[0930] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab7 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab7 or Fab fragments thereof may be produced via expression of Ab7 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0931] Antibody Ab9

[0932] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 281:

cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcaatagttatgca atgagctgggtccgccaggctccaggggaggggctggaatggatcggaatcattagtgatagtggtaggacatactacgcgagctgggcgaaag gccgattcaccatctccaaaacctcgaccacggtggatctgaaaatcaccagtccgacaaccgaggacacggccacctatttctgtgccagagag cccgagtacggctacgatgactatggtgattgggtttctgacttatggggcccaggcaccctcgtcaccgtctcgagcgcctccaccaagggccca tcggtcttcccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgac ggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgac cgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaa tcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacacc ctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgt ggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactg gctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccg agaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagc gacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctcta cagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcag aagagcctctccctgtctccgggtaaa (SEQ ID NO: 291).

[0933] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 282: cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcaatagttatgca atgagctgggtccgccaggctccaggggaggggctggaatggatcggaatcattagtgatagtggtaggacatactacgcgagctgggcgaaag gccgattcaccatctccaaaacctcgaccacggtggatctgaaaatcaccagtccgacaaccgaggacacggccacctatttctgtgccagagag cccgagtacggctacgatgactatggtgattgggtttctgacttatggggcccaggcaccctcgtcaccgtctcgagc (SEQ ID NO: 292).

[0934] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 290: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 300).

[0935] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 301:
gctgacgttgtgatgacccagactccagcctccgtggaggctgctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtag
ttacttatcctggtatcagcagaaaccagggcagcctcccaagctcctgatctatagggcatccactctggcatctggggtcccatcgcggttcaaag
gcagtggatctgggacacagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctattattatagtagtagtat
tacttatcgtaatgctttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagtt
gaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggt
aactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaa
acacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 311).

[0936] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 302:
gctgacgttgtgatgacccagactccagcctccgtggaggctgctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattagtag
ttacttatcctggtatcagcagaaaccagggcagcctcccaagctcctgatctatagggcatccactctggcatctggggtcccatcgcggttcaaag
gcagtggatctgggacacagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctattattatagtagtagtat
tacttatcgtaatgctttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 312).

[0937] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 310:
acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca
gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc
tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc
ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 320).

[0938] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 294; SEQ ID NO: 296; and SEQ ID NO: 298, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 281 or the variable heavy chain sequence of SEQ ID NO: 282, and/or one or more of the polynucleotide sequences of SEQ ID NO: 314; SEQ ID NO: 316 and SEQ ID NO: 318, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 301 or the variable light chain sequence of SEQ ID NO: 302, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding

one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0939] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 293; SEQ ID NO: 295; SEQ ID NO: 297; and SEQ ID NO: 299, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 281 or the variable heavy chain sequence of SEQ ID NO: 282, and/or one or more of the polynucleotide sequences of SEQ ID NO: 313; SEQ ID NO: 315; SEQ ID NO: 317; and SEQ ID NO: 319, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 301 or the variable light chain sequence of SEQ ID NO: 302, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0940] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 291 encoding the heavy chain sequence of SEQ ID NO: 281; the polynucleotide SEQ ID NO: 292 encoding the variable heavy chain sequence of SEQ ID NO: 282; the polynucleotide SEQ ID NO: 311 encoding the light chain sequence of SEQ ID NO: 301; the polynucleotide SEQ ID NO: 312 encoding the variable light chain sequence of SEQ ID NO: 302; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 294; SEQ ID NO: 296; and SEQ ID NO: 298) of the heavy chain sequence of SEQ ID NO: 281 or the variable heavy chain sequence of SEQ ID NO: 282; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 314; SEQ ID NO: 316; and SEQ ID NO: 318) of the light chain sequence of SEQ ID NO: 301 or the variable light chain sequence of SEQ ID NO: 302; polynucleotides encoding the framework regions (SEQ ID NO: 293; SEQ ID NO: 295; SEQ ID NO: 297; and SEQ ID NO: 299) of the heavy chain sequence of SEQ ID NO: 281 or the variable heavy chain sequence of SEQ ID NO: 282; and polynucleotides encoding the framework regions (SEQ ID NO: 313; SEQ ID NO: 315; SEQ ID NO: 317; and SEQ ID NO: 319) of the light chain sequence of SEQ ID NO: 301 or the variable light chain sequence of SEQ ID NO: 302.

[0941] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab9, the polynucleotides encoding the full

length Ab9 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 291 encoding the heavy chain sequence of SEQ ID NO: 281 and the polynucleotide SEQ ID NO: 311 encoding the light chain sequence of SEQ ID NO: 301.

[0942] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab9 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab9 or Fab fragments thereof may be produced via expression of Ab9 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0943] Antibody Ab10

[0944] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 321:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtagcgctga
catgatctgggtccgccaggctccagggaaggggctggaatccatcgggatgatttatgatgatggtgacacatactacgcgacttgggcgaaag
gccgattcaccatctccaaaacctcgaccacggtggatctgaagatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgt
gagtagtgtctggggccaggggaccctggtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccccctggcaccctcctccaagagca
cctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacct
acatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgc
ccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgc
gtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgg
gaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtct
ccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatccc
gggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggc
agccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtgg
cagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 331).

[0945] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 322:

cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggattctccctcagtagcgctga catgatctgggtccgccaggctccagggaaggggctggaatccatcgggatgatttatgatgatggtgacacatactacgcgacttgggcgaaag gccgattcaccatctccaaaaacctcgaccacggtggatctgaagatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgt gagtagtgtctggggccaggggaccctggtcaccgtctcgagc (SEQ ID NO: 332).

[0946] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 330: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 340).

[0947] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 341: gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaattgccaggccagtgagaacatttacaggtct ttagcctggtatcagcagaaaccagggcagcctcccaagctcctgatctactctgcatccactctggcatctggggtcccatcgcggttcaaaggca gtggatctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagtagt agttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagtt gaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggt aactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaa acacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 351).

[0948] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 342: gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaattgccaggccagtgagaacatttacaggtct ttagcctggtatcagcagaaaccagggcagcctcccaagctcctgatctactctgcatccactctggcatctggggtcccatcgcggttcaaaggca gtggatctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagtagt agttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 352).

[0949] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 350: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 360).

[0950] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 334; SEQ ID NO: 336; and SEQ ID NO: 338, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 321 or the variable heavy chain sequence of SEQ ID NO: 322, and/or one or more of the polynucleotide sequences of SEQ ID NO: 354; SEQ ID NO: 356 and SEQ ID NO: 358, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 341 or the variable light chain sequence of SEQ ID NO: 342, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0951] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 333; SEQ ID NO: 335; SEQ ID NO: 337; and SEQ ID NO: 339, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 321 or the variable heavy chain sequence of SEQ ID NO: 322, and/or one or more of the polynucleotide sequences of SEQ ID NO: 353; SEQ ID NO: 355; SEQ ID NO: 357; and SEQ ID NO: 359, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 341 or the variable light chain sequence of SEQ ID NO: 342, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0952] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH

comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 331 encoding the heavy chain sequence of SEQ ID NO: 321; the polynucleotide SEQ ID NO: 332 encoding the variable heavy chain sequence of SEQ ID NO: 322; the polynucleotide SEQ ID NO: 351 encoding the light chain sequence of SEQ ID NO: 341; the polynucleotide SEQ ID NO: 352 encoding the variable light chain sequence of SEQ ID NO: 342; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 334; SEQ ID NO: 336; and SEQ ID NO: 338) of the heavy chain sequence of SEQ ID NO: 321 or the variable heavy chain sequence of SEQ ID NO: 322; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 354; SEQ ID NO: 356; and SEQ ID NO: 358) of the light chain sequence of SEQ ID NO: 341 or the variable light chain sequence of SEQ ID NO: 342; polynucleotides encoding the framework regions (SEQ ID NO: 333; SEQ ID NO: 335; SEQ ID NO: 337; and SEQ ID NO: 339) of the heavy chain sequence of SEQ ID NO: 321 or the variable heavy chain sequence of SEQ ID NO: 322; and polynucleotides encoding the framework regions (SEQ ID NO: 353; SEQ ID NO: 355; SEQ ID NO: 357; and SEQ ID NO: 359) of the light chain sequence of SEQ ID NO: 341 or the variable light chain sequence of SEQ ID NO: 342.

[0953] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab10, the polynucleotides encoding the full length Ab10 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 331 encoding the heavy chain sequence of SEQ ID NO: 321 and the polynucleotide SEQ ID NO: 351 encoding the light chain sequence of SEQ ID NO: 341.

[0954] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab10 or Fab fragments thereof may be produced via expression of Ab10 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0955] Antibody Ab11

[0956] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 361:

cagtcgctggaggagtccgggggtcgcctggtcacgcctgggacatccctgacactcacctgcacagcctctggattctccctgagtgcctatgac atcctctgggtccgccaggctccagggaagggcctggaatccatcggaatgatgtatgatgatggtgacacatactacgcgacttgggcgaaagg ccgattcatcatctccagaacctcgaccacgatggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtg agtaatatctggggccaaggcaccctggtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccccctggcaccctcctccaagagcac ctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcgg cgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagaccta catctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcc cagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcg tggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggg aggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctc caacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccg ggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggca gccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggc agcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 371).

[0957] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 362: cagtcgctggaggagtccgggggtcgcctggtcacgcctgggacatccctgacactcacctgcacagcctctggattctccctgagtgcctatgac atcctctgggtccgccaggctccagggaagggcctggaatccatcggaatgatgtatgatgatggtgacacatactacgcgacttgggcgaaagg ccgattcatcatctccagaacctcgaccacgatggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtg agtaatatctggggccaaggcaccctggtcaccgtctcgagc (SEQ ID NO: 372).

[0958] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 370: gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 380).

[0959] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 381:
gacattgtgatgacccagattccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattgatagtag
cttggcctggtatcagcagaaaccagggcagcctcccaagctcctgatctattctgcatccactctggcatctggggtcccatcgcggttcaaaggc
agtggatctgggacagagttcactctcaccatcggcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagtag
ttattatggtattggtttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagtt
gaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggt
aactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaa
acacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 391).

[0960] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 382:
gacattgtgatgacccagattccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattgatagtag
cttggcctggtatcagcagaaaccagggcagcctcccaagctcctgatctattctgcatccactctggcatctggggtcccatcgcggttcaaaggc
agtggatctgggacagagttcactctcaccatcggcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagtag
ttattatggtattggtttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 392).

[0961] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 390:
acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca
gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc
tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc
ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 400).

[0962] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 374; SEQ ID NO: 376; and SEQ ID NO: 378, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 361 or the variable heavy chain sequence of SEQ ID NO: 362, and/or one or more of the polynucleotide sequences of SEQ ID NO: 394; SEQ ID NO: 396 and SEQ ID NO: 398, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 381 or the variable light chain sequence of SEQ ID NO: 382, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding

one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0963] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 373; SEQ ID NO: 375; SEQ ID NO: 377; and SEQ ID NO: 379, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 361 or the variable heavy chain sequence of SEQ ID NO: 362, and/or one or more of the polynucleotide sequences of SEQ ID NO: 393; SEQ ID NO: 395; SEQ ID NO: 397; and SEQ ID NO: 399, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 381 or the variable light chain sequence of SEQ ID NO: 382, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0964] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 371 encoding the heavy chain sequence of SEQ ID NO: 361; the polynucleotide SEQ ID NO: 372 encoding the variable heavy chain sequence of SEQ ID NO: 362; the polynucleotide SEQ ID NO: 391 encoding the light chain sequence of SEQ ID NO: 381; the polynucleotide SEQ ID NO: 392 encoding the variable light chain sequence of SEQ ID NO: 382; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 374; SEQ ID NO: 376; and SEQ ID NO: 378) of the heavy chain sequence of SEQ ID NO: 361 or the variable heavy chain sequence of SEQ ID NO: 362; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 394; SEQ ID NO: 396; and SEQ ID NO: 398) of the light chain sequence of SEQ ID NO: 381 or the variable light chain sequence of SEQ ID NO: 382; polynucleotides encoding the framework regions (SEQ ID NO: 373; SEQ ID NO: 375; SEQ ID NO: 377; and SEQ ID NO: 379) of the heavy chain sequence of SEQ ID NO: 361 or the variable heavy chain sequence of SEQ ID NO: 362; and polynucleotides encoding the framework regions (SEQ ID NO: 393; SEQ ID NO: 395; SEQ ID NO: 397; and SEQ ID NO: 399) of the light chain sequence of SEQ ID NO: 381 or the variable light chain sequence of SEQ ID NO: 382.

[0965] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab11, the polynucleotides encoding the full

length Ab11 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 371 encoding the heavy chain sequence of SEQ ID NO: 361 and the polynucleotide SEQ ID NO: 391 encoding the light chain sequence of SEQ ID NO: 381.

[0966] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab11 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab11 or Fab fragments thereof may be produced via expression of Ab11 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0967] Antibody Ab12

[0968] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 401:
cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggatcctccctcagtgattatgac
atgatctgggtccgccaggctccagggaaggggctggaatccatcgggatcatttatgatgatggtgacacatactacgcgacttgggcgaaagg
ccgattcaccatctccaaaacctcgaccacggtggatctgagaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtg
agtaatatgtggggcccggggaccctggtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccccctggcaccctcctccaagagcac
ctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcgg
cgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagaccta
catctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcc
cagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcg
tggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggg
aggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctc
caacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccg
ggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggca
gccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggc
agcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 411).

[0969] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 402:

cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggatcctccctcagtgattatgac atgatctgggtccgccaggctccagggaaggggctggaatccatcgggatcatttatgatgatggtgacacatactacgcgacttgggcgaaagg ccgattcaccatctccaaaacctcgaccacggtggatctgagaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaaggtgtg agtaatatgtggggcccggggaccctggtcaccgtctcgagc (SEQ ID NO: 412).

[0970] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 410: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 420).

[0971] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 421: gacgtcgtgatgacccagactccatcctccgtgtctgcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattggtagtagc ttagcctggtatcagcagaaaccagggcagcgtcccaagctcctgatctatgctgcatccactctggcatctggggtcccatcgcggttcaaaggca gtggatctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagtagt agttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagtt gaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggt aactcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaa acacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 431).

[0972] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 422: gacgtcgtgatgacccagactccatcctccgtgtctgcagctgtgggaggcacagtcaccatcaagtgccaggccagtcagagcattggtagtagc ttagcctggtatcagcagaaaccagggcagcgtcccaagctcctgatctatgctgcatccactctggcatctggggtcccatcgcggttcaaaggca gtggatctgggacagagttcactctcaccatcagcgacctggagtgtgccgatgctgccacttactactgtcaaagctatgatggtagtagtagtagt agttatggtgttggtttcggcggagggaccgaggtggtggtcaaacgt (SEQ ID NO: 432).

[0973] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 430: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 440).

[0974] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 414; SEQ ID NO: 416; and SEQ ID NO: 418, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 401 or the variable heavy chain sequence of SEQ ID NO: 402, and/or one or more of the polynucleotide sequences of SEQ ID NO: 434; SEQ ID NO: 436 and SEQ ID NO: 438, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 421 or the variable light chain sequence of SEQ ID NO: 422, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0975] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 413; SEQ ID NO: 415; SEQ ID NO: 417; and SEQ ID NO: 419, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 401 or the variable heavy chain sequence of SEQ ID NO: 402, and/or one or more of the polynucleotide sequences of SEQ ID NO: 433; SEQ ID NO: 435; SEQ ID NO: 437; and SEQ ID NO: 439, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 421 or the variable light chain sequence of SEQ ID NO: 422, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0976] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH

comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 411 encoding the heavy chain sequence of SEQ ID NO: 401; the polynucleotide SEQ ID NO: 412 encoding the variable heavy chain sequence of SEQ ID NO: 402; the polynucleotide SEQ ID NO: 431 encoding the light chain sequence of SEQ ID NO: 421; the polynucleotide SEQ ID NO: 432 encoding the variable light chain sequence of SEQ ID NO: 422; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 414; SEQ ID NO: 416; and SEQ ID NO: 418) of the heavy chain sequence of SEQ ID NO: 401 or the variable heavy chain sequence of SEQ ID NO: 402; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 434; SEQ ID NO: 436; and SEQ ID NO: 438) of the light chain sequence of SEQ ID NO: 421 or the variable light chain sequence of SEQ ID NO: 422; polynucleotides encoding the framework regions (SEQ ID NO: 413; SEQ ID NO: 415; SEQ ID NO: 417; and SEQ ID NO: 419) of the heavy chain sequence of SEQ ID NO: 401 or the variable heavy chain sequence of SEQ ID NO: 402; and polynucleotides encoding the framework regions (SEQ ID NO: 433; SEQ ID NO: 435; SEQ ID NO: 437; and SEQ ID NO: 439) of the light chain sequence of SEQ ID NO: 421 or the variable light chain sequence of SEQ ID NO: 422.

[0977] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab12, the polynucleotides encoding the full length Ab12 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 411 encoding the heavy chain sequence of SEQ ID NO: 401 and the polynucleotide SEQ ID NO: 431 encoding the light chain sequence of SEQ ID NO: 421.

[0978] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab12 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab12 or Fab fragments thereof may be produced via expression of Ab12 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0979] Antibody Ab1.H

[0980] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 441:

gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtaactat gacatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatgatttatgatgatggtgacacatactacgctagttctgctaaag gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa ggtgtgagtaatcactggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccctggcaccctcctccaa gagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgacc agcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccag acctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccacc gtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcac atgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccg cgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaag gtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccat cccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatg ggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcag gtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 451).

[0981] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 442: gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtaactat gacatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatgatttatgatgatggtgacacatactacgctagttctgctaaag gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa ggtgtgagtaatcactggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 452).

[0982] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 450: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 460).

[0983] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 461:
gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattagtagttactta
gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagtg
gatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtggtagtagtta
tggtgttggtttcggcggaggaaccaaggtggaaatcaaacgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaat
ctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactc
ccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacaca
aagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 471).

[0984] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 462:
gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattagtagttactta
gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagtg
gatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtggtagtagtta
tggtgttggtttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 472).

[0985] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 470:
acggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccag
agaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcaccta
cagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcc
cgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 480).

[0986] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 454; SEQ ID NO: 456; and SEQ ID NO: 458, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 441 or the variable heavy chain sequence of SEQ ID NO: 442, and/or one or more of the polynucleotide sequences of SEQ ID NO: 474; SEQ ID NO: 476 and SEQ ID NO: 478, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 461 or the variable light chain sequence of SEQ ID NO: 462, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding

one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0987] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 453; SEQ ID NO: 455; SEQ ID NO: 457; and SEQ ID NO: 459, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 441 or the variable heavy chain sequence of SEQ ID NO: 442, and/or one or more of the polynucleotide sequences of SEQ ID NO: 473; SEQ ID NO: 475; SEQ ID NO: 477; and SEQ ID NO: 479, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 461 or the variable light chain sequence of SEQ ID NO: 462, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0988] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 451 encoding the heavy chain sequence of SEQ ID NO: 441; the polynucleotide SEQ ID NO: 452 encoding the variable heavy chain sequence of SEQ ID NO: 442; the polynucleotide SEQ ID NO: 471 encoding the light chain sequence of SEQ ID NO: 461; the polynucleotide SEQ ID NO: 472 encoding the variable light chain sequence of SEQ ID NO: 462; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 454; SEQ ID NO: 456; and SEQ ID NO: 458) of the heavy chain sequence of SEQ ID NO: 441 or the variable heavy chain sequence of SEQ ID NO: 442; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 474; SEQ ID NO: 476; and SEQ ID NO: 478) of the light chain sequence of SEQ ID NO: 461 or the variable light chain sequence of SEQ ID NO: 462; polynucleotides encoding the framework regions (SEQ ID NO: 453; SEQ ID NO: 455; SEQ ID NO: 457; and SEQ ID NO: 459) of the heavy chain sequence of SEQ ID NO: 441 or the variable heavy chain sequence of SEQ ID NO: 442; and polynucleotides encoding the framework regions (SEQ ID NO: 473; SEQ ID NO: 475; SEQ ID NO: 477; and SEQ ID NO: 479) of the light chain sequence of SEQ ID NO: 461 or the variable light chain sequence of SEQ ID NO: 462.

[0989] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab1.H, the polynucleotides encoding the full

length Ab1.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 451 encoding the heavy chain sequence of SEQ ID NO: 441 and the polynucleotide SEQ ID NO: 471 encoding the light chain sequence of SEQ ID NO: 461.

[0990] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab1.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab1.H or Fab fragments thereof may be produced via expression of Ab1.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[0991] Antibody Ab2.H

[0992] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 481:
gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtaagtat
gacatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatcatttatgatgatggcgacacatattacgctagttctgctaaag
gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
ggtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccctggcaccctcctccaag
agcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgacca
gcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccaga
cctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccg
tgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggacccctgaggtcaca
tgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgc
gggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggt
ctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgccccatc
ccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgg
gcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggt
ggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa
(SEQ ID NO: 491).

[0993] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 482:

gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtaagtat gacatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatcatttatgatgatggcgacacatattacgctagttctgctaaag gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa ggtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 492).

[0994] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 490: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 500).

[0995] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 501: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattagtaactactta gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagtg gatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgagggtagtagtagtagtagtta tggtgttggtttcggcggaggaaccaaggtggaaatcaaacgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaat ctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactc ccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacaca aagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 511).

[0996] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 502: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattagtaactactta gcctggtatcagcagaaaccaggaaaagccccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagtg gatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgagggtagtagtagtagtagtta tggtgttggtttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 512).

[0997] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 510: acggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccag agaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcaccta cagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcc cgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 520).

[0998] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 494; SEQ ID NO: 496; and SEQ ID NO: 498, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 481 or the variable heavy chain sequence of SEQ ID NO: 482, and/or one or more of the polynucleotide sequences of SEQ ID NO: 514; SEQ ID NO: 516 and SEQ ID NO: 518, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 501 or the variable light chain sequence of SEQ ID NO: 502, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[0999] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 493; SEQ ID NO: 495; SEQ ID NO: 497; and SEQ ID NO: 499, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 481 or the variable heavy chain sequence of SEQ ID NO: 482, and/or one or more of the polynucleotide sequences of SEQ ID NO: 513; SEQ ID NO: 515; SEQ ID NO: 517; and SEQ ID NO: 519, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 501 or the variable light chain sequence of SEQ ID NO: 502, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1000] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH

comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 491 encoding the heavy chain sequence of SEQ ID NO: 481; the polynucleotide SEQ ID NO: 492 encoding the variable heavy chain sequence of SEQ ID NO: 482; the polynucleotide SEQ ID NO: 511 encoding the light chain sequence of SEQ ID NO: 501; the polynucleotide SEQ ID NO: 512 encoding the variable light chain sequence of SEQ ID NO: 502; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 494; SEQ ID NO: 496; and SEQ ID NO: 498) of the heavy chain sequence of SEQ ID NO: 481 or the variable heavy chain sequence of SEQ ID NO: 482; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 514; SEQ ID NO: 516; and SEQ ID NO: 518) of the light chain sequence of SEQ ID NO: 501 or the variable light chain sequence of SEQ ID NO: 502; polynucleotides encoding the framework regions (SEQ ID NO: 493; SEQ ID NO: 495; SEQ ID NO: 497; and SEQ ID NO: 499) of the heavy chain sequence of SEQ ID NO: 481 or the variable heavy chain sequence of SEQ ID NO: 482; and polynucleotides encoding the framework regions (SEQ ID NO: 513; SEQ ID NO: 515; SEQ ID NO: 517; and SEQ ID NO: 519) of the light chain sequence of SEQ ID NO: 501 or the variable light chain sequence of SEQ ID NO: 502.

[1001] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab2.H, the polynucleotides encoding the full length Ab2.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 491 encoding the heavy chain sequence of SEQ ID NO: 481 and the polynucleotide SEQ ID NO: 511 encoding the light chain sequence of SEQ ID NO: 501.

[1002] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab2.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab2.H or Fab fragments thereof may be produced via expression of Ab2.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1003] Antibody Ab3.H

[1004] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 521:

gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggttcctccctcagtaactttg
acatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatcatttatgattttggtagcacatactacgccagctctgctaaagg
ccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaag
gtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccccctggcaccctcctccaaga
gcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccag
cggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagac
ctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgt
gcccagcacctgaactcctgggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacat
gcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgc
gggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggt
ctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatc
ccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgg
gcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggt
ggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa
(SEQ ID NO: 531).

[1005] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 522:
gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggttcctccctcagtaactttg
acatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatcatttatgattttggtagcacatactacgccagctctgctaaagg
ccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaag
gtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 532).

[1006] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 530:
gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact
acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact
ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga
cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc
cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc
accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca
aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg
gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact
ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc
tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 540).

[1007] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 541:
gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtgaggatattagtagtaactta
gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagtg
gatctggaacagaatttactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagtagttat
ggtattggtttcggcggaggaaccaaggtggaaatcaaacgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatc
tggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcc
caggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaa
agtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 551).

[1008] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 542:
gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtgaggatattagtagtaactta
gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagtg
gatctggaacagaatttactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagtagttat
ggtattggtttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 552).

[1009] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 550:
acggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccag
agaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcaccta
cagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcc
cgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 560).

[1010] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 534; SEQ ID NO: 536; and SEQ ID NO: 538, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 521 or the variable heavy chain sequence of SEQ ID NO: 522, and/or one or more of the polynucleotide sequences of SEQ ID NO: 554; SEQ ID NO: 556 and SEQ ID NO: 558, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 541 or the variable light chain sequence of SEQ ID NO: 542, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding

one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1011] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 533; SEQ ID NO: 535; SEQ ID NO: 537; and SEQ ID NO: 539, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 521 or the variable heavy chain sequence of SEQ ID NO: 522, and/or one or more of the polynucleotide sequences of SEQ ID NO: 553; SEQ ID NO: 555; SEQ ID NO: 557; and SEQ ID NO: 559, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 541 or the variable light chain sequence of SEQ ID NO: 542, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1012] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 531 encoding the heavy chain sequence of SEQ ID NO: 521; the polynucleotide SEQ ID NO: 532 encoding the variable heavy chain sequence of SEQ ID NO: 522; the polynucleotide SEQ ID NO: 551 encoding the light chain sequence of SEQ ID NO: 541; the polynucleotide SEQ ID NO: 552 encoding the variable light chain sequence of SEQ ID NO: 542; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 534; SEQ ID NO: 536; and SEQ ID NO: 538) of the heavy chain sequence of SEQ ID NO: 521 or the variable heavy chain sequence of SEQ ID NO: 522; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 554; SEQ ID NO: 556; and SEQ ID NO: 558) of the light chain sequence of SEQ ID NO: 541 or the variable light chain sequence of SEQ ID NO: 542; polynucleotides encoding the framework regions (SEQ ID NO: 533; SEQ ID NO: 535; SEQ ID NO: 537; and SEQ ID NO: 539) of the heavy chain sequence of SEQ ID NO: 521 or the variable heavy chain sequence of SEQ ID NO: 522; and polynucleotides encoding the framework regions (SEQ ID NO: 553; SEQ ID NO: 555; SEQ ID NO: 557; and SEQ ID NO: 559) of the light chain sequence of SEQ ID NO: 541 or the variable light chain sequence of SEQ ID NO: 542.

[1013] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab3.H, the polynucleotides encoding the full

length Ab3.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 531 encoding the heavy chain sequence of SEQ ID NO: 521 and the polynucleotide SEQ ID NO: 551 encoding the light chain sequence of SEQ ID NO: 541.

[1014] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab3.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab3.H or Fab fragments thereof may be produced via expression of Ab3.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1015] Antibody Ab4.H

[1016] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 561:
gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtaagcat
gacatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatcatttatgatgatggtgatacatactacgctaattctgctaaagg
ccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaag
gtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccctggcaccctcctccaaga
gcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccag
cggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagac
ctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgt
gcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccccaaaacccaaggacaccctcatgatctcccggacccctgaggtcacat
gcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgc
gggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggt
ctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatc
ccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgg
gcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggt
ggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa
(SEQ ID NO: 571).

[1017] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 562:

gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtaagcat gacatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatcatttatgatgatggtgatacatactacgctaattctgctaaagg ccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaag gtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 572).

[1018] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 570: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 580).

[1019] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 581: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtagagccagtcagagcattagtgtctacct cgcctggtatcagcagaaaccaggaaaagccccctaagctcctgatctatcaggcatccaaactggcctctggagtcccatcaaggttcagcggca gtggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagtagtag ttatggtgttggtttcggcggaggaaccaaggtggaaatcaaacgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaa atctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaact cccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacac aaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 591).

[1020] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 582: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtagagccagtcagagcattagtgtctacct cgcctggtatcagcagaaaccaggaaaagccccctaagctcctgatctatcaggcatccaaactggcctctggagtcccatcaaggttcagcggca gtggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagtagtag ttatggtgttggtttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 592).

[1021] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 590: acggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccag agaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcaccta cagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcc cgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 600).

[1022] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 574; SEQ ID NO: 576; and SEQ ID NO: 578, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 561 or the variable heavy chain sequence of SEQ ID NO: 562, and/or one or more of the polynucleotide sequences of SEQ ID NO: 594; SEQ ID NO: 596 and SEQ ID NO: 598, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 581 or the variable light chain sequence of SEQ ID NO: 582, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1023] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 573; SEQ ID NO: 575; SEQ ID NO: 577; and SEQ ID NO: 579, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 561 or the variable heavy chain sequence of SEQ ID NO: 562, and/or one or more of the polynucleotide sequences of SEQ ID NO: 593; SEQ ID NO: 595; SEQ ID NO: 597; and SEQ ID NO: 599, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 581 or the variable light chain sequence of SEQ ID NO: 582, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1024] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH

comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 571 encoding the heavy chain sequence of SEQ ID NO: 561; the polynucleotide SEQ ID NO: 572 encoding the variable heavy chain sequence of SEQ ID NO: 562; the polynucleotide SEQ ID NO: 591 encoding the light chain sequence of SEQ ID NO: 581; the polynucleotide SEQ ID NO: 592 encoding the variable light chain sequence of SEQ ID NO: 582; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 574; SEQ ID NO: 576; and SEQ ID NO: 578) of the heavy chain sequence of SEQ ID NO: 561 or the variable heavy chain sequence of SEQ ID NO: 562; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 594; SEQ ID NO: 596; and SEQ ID NO: 598) of the light chain sequence of SEQ ID NO: 581 or the variable light chain sequence of SEQ ID NO: 582; polynucleotides encoding the framework regions (SEQ ID NO: 573; SEQ ID NO: 575; SEQ ID NO: 577; and SEQ ID NO: 579) of the heavy chain sequence of SEQ ID NO: 561 or the variable heavy chain sequence of SEQ ID NO: 562; and polynucleotides encoding the framework regions (SEQ ID NO: 593; SEQ ID NO: 595; SEQ ID NO: 597; and SEQ ID NO: 599) of the light chain sequence of SEQ ID NO: 581 or the variable light chain sequence of SEQ ID NO: 582.

[1025] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab4.H, the polynucleotides encoding the full length Ab4.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 571 encoding the heavy chain sequence of SEQ ID NO: 561 and the polynucleotide SEQ ID NO: 591 encoding the light chain sequence of SEQ ID NO: 581.

[1026] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab4.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab4.H or Fab fragments thereof may be produced via expression of Ab4.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1027] Antibody Ab6.H

[1028] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 601:

gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattctccctcactgactatg caatgagctgggtccgtcaggctccagggaaggggctggagtggatcggaatcattagtgatagtggtagcacatactacgctagctctgctaaag gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctaga gagcccgagtacggctacgatgagtatggtgattgggtttctgacttatggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggc ccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggt gacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggt gaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcc caaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggacccgtcagtcttcctcttcccccaaaacccaagga caccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacg gcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccagg actggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagc cccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttc ctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacac gcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 611).

[1029] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 602: gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattctccctcactgactatg caatgagctgggtccgtcaggctccagggaaggggctggagtggatcggaatcattagtgatagtggtagcacatactacgctagctctgctaaag gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctaga gagcccgagtacggctacgatgagtatggtgattgggtttctgacttatggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 612).

[1030] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 610: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggacccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact

ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 620).

[1031] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 621: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccactcagagcattggtaataactta gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctatagggcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctattactatagtagtagtattacttat cataatgctttcggcggaggaaccaaggtggaaatcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatc tggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcc caggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaa agtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 631).

[1032] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 622: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccactcagagcattggtaataactta gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctatagggcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctattactatagtagtagtattacttat cataatgctttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 632).

[1033] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 630: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 640).

[1034] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 614; SEQ ID NO: 616; and SEQ ID NO: 618, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 601 or the variable heavy chain sequence of SEQ ID NO: 602, and/or one or more of the polynucleotide sequences of SEQ ID NO: 634; SEQ ID NO: 636 and SEQ ID NO: 638, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 621 or the variable light chain sequence of SEQ ID NO: 622, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention

or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1035] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 613; SEQ ID NO: 615; SEQ ID NO: 617; and SEQ ID NO: 619, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 601 or the variable heavy chain sequence of SEQ ID NO: 602, and/or one or more of the polynucleotide sequences of SEQ ID NO: 633; SEQ ID NO: 635; SEQ ID NO: 637; and SEQ ID NO: 639, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 621 or the variable light chain sequence of SEQ ID NO: 622, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1036] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 611 encoding the heavy chain sequence of SEQ ID NO: 601; the polynucleotide SEQ ID NO: 612 encoding the variable heavy chain sequence of SEQ ID NO: 602; the polynucleotide SEQ ID NO: 631 encoding the light chain sequence of SEQ ID NO: 621; the polynucleotide SEQ ID NO: 632 encoding the variable light chain sequence of SEQ ID NO: 622; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 614; SEQ ID NO: 616; and SEQ ID NO: 618) of the heavy chain sequence of SEQ ID NO: 601 or the variable heavy chain sequence of SEQ ID NO: 602; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 634; SEQ ID NO: 636; and SEQ ID NO: 638) of the light chain sequence of SEQ ID NO: 621 or the variable light chain sequence of SEQ ID NO: 622; polynucleotides encoding the framework regions (SEQ ID NO: 613; SEQ ID NO: 615; SEQ ID NO: 617; and SEQ ID NO: 619) of the heavy chain sequence of SEQ ID NO: 601 or the variable heavy chain sequence of SEQ ID NO: 602; and polynucleotides encoding the framework regions (SEQ ID NO: 633; SEQ ID NO: 635; SEQ ID NO: 637; and SEQ ID NO: 639) of the light chain sequence of SEQ ID NO: 621 or the variable light chain sequence of SEQ ID NO: 622.

[1037] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having

binding specificity for ACTH. With respect to antibody Ab6.H, the polynucleotides encoding the full length Ab6.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 611 encoding the heavy chain sequence of SEQ ID NO: 601 and the polynucleotide SEQ ID NO: 631 encoding the light chain sequence of SEQ ID NO: 621.

[1038] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab6.H or Fab fragments thereof may be produced via expression of Ab6.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1039] Antibody Ab7.H

[1040] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 641:
gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattctccctcagtagctatg
caatgagctgggtccgtcaggctccagggaaggggctggagtggatcggaatcattagtgatagtggtagcacatactacgcgagctctgctaaa
ggccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctag
agagcccgagtacggctacgatgactatggtgattgggtttctgacttatggggccaagggaccctcgtcaccgtctcgagcgcctccaccaaggg
cccatcggtcttcccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccgg
tgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtgg
tgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcc
caaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaagga
caccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacg
gcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccagg
actggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagc
cccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcc
cagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttc
ctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacac
gcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 651).

[1041] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain

polypeptide sequence of SEQ ID NO: 642: gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattctccctcagtagctatg caatgagctgggtccgtcaggctccagggaaggggctggagtggatcggaatcattagtgatagtggtagcacatactacgcgagctctgctaaa ggccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctag agagcccgagtacggctacgatgactatggtgattgggtttctgacttatggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 652).

[1042] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 650: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 660).

[1043] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 661: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattagtgattactta tcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctatagggcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctattactatagtagtagtattacttat cgtaatgctttcggcggaggaaccaaggtggaaatcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaat ctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactc ccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacaca aagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 671).

[1044] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 662: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattagtgattactta tcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctatagggcatccactctggcatctggagtcccatcaaggttcagcggcagt

ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctattactatagtagtagtattacttat cgtaatgctttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 672).

[1045] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 670: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 680).

[1046] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 654; SEQ ID NO: 656; and SEQ ID NO: 658, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 641 or the variable heavy chain sequence of SEQ ID NO: 642, and/or one or more of the polynucleotide sequences of SEQ ID NO: 674; SEQ ID NO: 676 and SEQ ID NO: 678, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 661 or the variable light chain sequence of SEQ ID NO: 662, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1047] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 653; SEQ ID NO: 655; SEQ ID NO: 657; and SEQ ID NO: 659, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 641 or the variable heavy chain sequence of SEQ ID NO: 642, and/or one or more of the polynucleotide sequences of SEQ ID NO: 673; SEQ ID NO: 675; SEQ ID NO: 677; and SEQ ID NO: 679, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 661 or the variable light chain sequence of SEQ ID NO: 662, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1048] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 651 encoding the heavy chain sequence of SEQ ID NO: 641; the polynucleotide SEQ ID NO: 652 encoding the variable heavy chain sequence of SEQ ID NO: 642; the polynucleotide SEQ ID NO: 671 encoding the light chain sequence of SEQ ID NO: 661; the polynucleotide SEQ ID NO: 672 encoding the variable light chain sequence of SEQ ID NO: 662; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 654; SEQ ID NO: 656; and SEQ ID NO: 658) of the heavy chain sequence of SEQ ID NO: 641 or the variable heavy chain sequence of SEQ ID NO: 642; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 674; SEQ ID NO: 676; and SEQ ID NO: 678) of the light chain sequence of SEQ ID NO: 661 or the variable light chain sequence of SEQ ID NO: 662; polynucleotides encoding the framework regions (SEQ ID NO: 653; SEQ ID NO: 655; SEQ ID NO: 657; and SEQ ID NO: 659) of the heavy chain sequence of SEQ ID NO: 641 or the variable heavy chain sequence of SEQ ID NO: 642; and polynucleotides encoding the framework regions (SEQ ID NO: 673; SEQ ID NO: 675; SEQ ID NO: 677; and SEQ ID NO: 679) of the light chain sequence of SEQ ID NO: 661 or the variable light chain sequence of SEQ ID NO: 662.

[1049] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab7.H, the polynucleotides encoding the full length Ab7.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 651 encoding the heavy chain sequence of SEQ ID NO: 641 and the polynucleotide SEQ ID NO: 671 encoding the light chain sequence of SEQ ID NO: 661.

[1050] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab7.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab7.H or Fab fragments thereof may be produced via expression of Ab7.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1051] Antibody Ab7A.H

[1052] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 681: gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattctccctcagtagctatg caatgagctgggtccgtcaggctccagggaaggggctggagtggatcggaatcattagtgatagtggtagcacatactacgcgagctctgctaaa ggccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctag agagcccgagtacggctacgatgactatggtgattgggtttctgacttatggggccaagggaccctcgtcaccgtctcgagcgcctccaccaaggg cccatcggtcttcccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccgg tgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtgg tgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcc caaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaagga caccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacg gcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccagg actggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagc cccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttc ctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacac gcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 691).

[1053] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 682: gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattctccctcagtagctatg caatgagctgggtccgtcaggctccagggaaggggctggagtggatcggaatcattagtgatagtggtagcacatactacgcgagctctgctaaa ggccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctag agagcccgagtacggctacgatgactatggtgattgggtttctgacttatggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 692).

[1054] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 690: gcctccaccaagggcccatcggtcttcccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc

accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 700).

[1055] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 701: gctgacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattagtgatta cttatcctggtatcagcagaaaccaggaaaagccccctaagctcctgatctatagggcatccactctggcatctggagtcccatcaaggttcagcggc agtggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctattactatagtagtagttac ttatcgtaatgctttcggcggaggaaccaaggtggaaatcaaacgtacggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttga aatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaa ctcccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaac acaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 711).

[1056] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 702: gctgacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattagtgatta cttatcctggtatcagcagaaaccaggaaaagccccctaagctcctgatctatagggcatccactctggcatctggagtcccatcaaggttcagcggc agtggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctattactatagtagtagttac ttatcgtaatgctttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 712).

[1057] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 710: acggtagcggccccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatccca gagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcacc tacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgc ccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 720).

[1058] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 694; SEQ ID NO: 696; and SEQ ID NO: 698, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 681 or the variable heavy chain sequence of SEQ ID NO: 682, and/or one or more of the polynucleotide sequences of SEQ ID NO:

714; SEQ ID NO: 716 and SEQ ID NO: 718, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 701 or the variable light chain sequence of SEQ ID NO: 702, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1059] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 693; SEQ ID NO: 695; SEQ ID NO: 697; and SEQ ID NO: 699, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 681 or the variable heavy chain sequence of SEQ ID NO: 682, and/or one or more of the polynucleotide sequences of SEQ ID NO: 713; SEQ ID NO: 715; SEQ ID NO: 717; and SEQ ID NO: 719, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 701 or the variable light chain sequence of SEQ ID NO: 702, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1060] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 691 encoding the heavy chain sequence of SEQ ID NO: 681; the polynucleotide SEQ ID NO: 692 encoding the variable heavy chain sequence of SEQ ID NO: 682; the polynucleotide SEQ ID NO: 711 encoding the light chain sequence of SEQ ID NO: 701; the polynucleotide SEQ ID NO: 712 encoding the variable light chain sequence of SEQ ID NO: 702; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 694; SEQ ID NO: 696; and SEQ ID NO: 698) of the heavy chain sequence of SEQ ID NO: 681 or the variable heavy chain sequence of SEQ ID NO: 682; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 714; SEQ ID NO: 716; and SEQ ID NO: 718) of the light chain sequence of SEQ ID NO: 701 or the variable light chain sequence of SEQ ID NO: 702; polynucleotides encoding the framework regions (SEQ ID NO: 693; SEQ ID NO: 695; SEQ ID NO: 697; and SEQ ID NO: 699) of the heavy chain sequence of SEQ ID NO: 681 or the variable heavy chain sequence of SEQ ID NO: 682; and polynucleotides encoding the framework regions

(SEQ ID NO: 713; SEQ ID NO: 715; SEQ ID NO: 717; and SEQ ID NO: 719) of the light chain sequence of SEQ ID NO: 701 or the variable light chain sequence of SEQ ID NO: 702.

[1061] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab7A.H, the polynucleotides encoding the full length Ab7A.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 691 encoding the heavy chain sequence of SEQ ID NO: 681 and the polynucleotide SEQ ID NO: 711 encoding the light chain sequence of SEQ ID NO: 701.

[1062] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab7A.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab7A.H or Fab fragments thereof may be produced via expression of Ab7A.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1063] Antibody Ab10.H

[1064] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 721:

gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtagcgct
gacatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatgatttatgatgatggtgacacatactacgctacttctgctaaag
gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
ggtgtgagtagtgtctggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccccctggcaccctcctccaa
gagcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgacc
agcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccag
acctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccacc
gtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcac
atgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccg
cgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaag
gtctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccat
cccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatg
ggcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcag

gtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 731).

[1065] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 722: gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtagcgct gacatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatgatttatgatgatggtgacacatactacgctacttctgctaaag gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa ggtgtgagtagtgtctggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 732).

[1066] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 730: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc cccaaaacccaaggacaccctcatgatctcccggaccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 740).

[1067] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 741: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtgagaacatttacaggtcttta gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagtg gatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagtagttat ggtgttggtttcggcggaggaaccaaggtggaaatcaaacgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatc tggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcc caggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaa agtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 751).

[1068] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 742:

gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtgagaacatttacaggtcttta gcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagtg gatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagtagttat ggtgttggtttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 752).

[1069] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 750: acggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccag agaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcaccta cagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcc cgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 760).

[1070] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 734; SEQ ID NO: 736; and SEQ ID NO: 738, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 721 or the variable heavy chain sequence of SEQ ID NO: 722, and/or one or more of the polynucleotide sequences of SEQ ID NO: 754; SEQ ID NO: 756 and SEQ ID NO: 758, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 741 or the variable light chain sequence of SEQ ID NO: 742, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1071] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 733; SEQ ID NO: 735; SEQ ID NO: 737; and SEQ ID NO: 739, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 721 or the variable heavy chain sequence of SEQ ID NO: 722, and/or one or more of the polynucleotide sequences of SEQ ID NO: 753; SEQ ID NO: 755; SEQ ID NO: 757; and SEQ ID NO: 759, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 741 or the variable light chain sequence of SEQ ID NO: 742, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and

variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1072] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 731 encoding the heavy chain sequence of SEQ ID NO: 721; the polynucleotide SEQ ID NO: 732 encoding the variable heavy chain sequence of SEQ ID NO: 722; the polynucleotide SEQ ID NO: 751 encoding the light chain sequence of SEQ ID NO: 741; the polynucleotide SEQ ID NO: 752 encoding the variable light chain sequence of SEQ ID NO: 742; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 734; SEQ ID NO: 736; and SEQ ID NO: 738) of the heavy chain sequence of SEQ ID NO: 721 or the variable heavy chain sequence of SEQ ID NO: 722; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 754; SEQ ID NO: 756; and SEQ ID NO: 758) of the light chain sequence of SEQ ID NO: 741 or the variable light chain sequence of SEQ ID NO: 742; polynucleotides encoding the framework regions (SEQ ID NO: 733; SEQ ID NO: 735; SEQ ID NO: 737; and SEQ ID NO: 739) of the heavy chain sequence of SEQ ID NO: 721 or the variable heavy chain sequence of SEQ ID NO: 722; and polynucleotides encoding the framework regions (SEQ ID NO: 753; SEQ ID NO: 755; SEQ ID NO: 757; and SEQ ID NO: 759) of the light chain sequence of SEQ ID NO: 741 or the variable light chain sequence of SEQ ID NO: 742.

[1073] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab10.H, the polynucleotides encoding the full length Ab10.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 731 encoding the heavy chain sequence of SEQ ID NO: 721 and the polynucleotide SEQ ID NO: 751 encoding the light chain sequence of SEQ ID NO: 741.

[1074] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab10.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab10.H or Fab fragments thereof may be produced via expression of Ab10.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1075] Antibody Ab11.H

[1076] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 761:
gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtgcctat
gacatcctctgggtccgtcaggctccagggaaggggctggagtccatcggaatgatgtatgatgatggtgacacatactacgctacttctgctaaag
gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
ggtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccctggcaccctcctccaag
agcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgacca
gcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccaga
cctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccg
tgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcaca
tgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgc
gggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggt
ctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatc
ccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgg
gcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggt
ggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa
(SEQ ID NO: 771).

[1077] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 762:
gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtgcctat
gacatcctctgggtccgtcaggctccagggaaggggctggagtccatcggaatgatgtatgatgatggtgacacatactacgctacttctgctaaag
gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
ggtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 772).

[1078] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 770:
gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact
acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact
ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga
cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc
cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc

accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 780).

[1079] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 781: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattgatagtagctt ggcctggtatcagcagaaaccaggaaaagccccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagttact atggtattggtttcggcggaggaaccaaggtggaaatcaaacgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaa tctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactc ccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacaca aagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 791).

[1080] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 782: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattgatagtagctt ggcctggtatcagcagaaaccaggaaaagccccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagttact atggtattggtttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 792).

[1081] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 790: acggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccag agaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcaccta cagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcc cgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 800).

[1082] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 774; SEQ ID NO: 776; and SEQ ID NO: 778, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 761 or the variable heavy chain sequence of SEQ ID NO: 762, and/or one or more of the polynucleotide sequences of SEQ ID NO: 794; SEQ ID NO: 796 and SEQ ID NO: 798, which correspond to the complementarity-determining

regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 781 or the variable light chain sequence of SEQ ID NO: 782, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1083] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 773; SEQ ID NO: 775; SEQ ID NO: 777; and SEQ ID NO: 779, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 761 or the variable heavy chain sequence of SEQ ID NO: 762, and/or one or more of the polynucleotide sequences of SEQ ID NO: 793; SEQ ID NO: 795; SEQ ID NO: 797; and SEQ ID NO: 799, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 781 or the variable light chain sequence of SEQ ID NO: 782, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1084] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 771 encoding the heavy chain sequence of SEQ ID NO: 761; the polynucleotide SEQ ID NO: 772 encoding the variable heavy chain sequence of SEQ ID NO: 762; the polynucleotide SEQ ID NO: 791 encoding the light chain sequence of SEQ ID NO: 781; the polynucleotide SEQ ID NO: 792 encoding the variable light chain sequence of SEQ ID NO: 782; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 774; SEQ ID NO: 776; and SEQ ID NO: 778) of the heavy chain sequence of SEQ ID NO: 761 or the variable heavy chain sequence of SEQ ID NO: 762; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 794; SEQ ID NO: 796; and SEQ ID NO: 798) of the light chain sequence of SEQ ID NO: 781 or the variable light chain sequence of SEQ ID NO: 782; polynucleotides encoding the framework regions (SEQ ID NO: 773; SEQ ID NO: 775; SEQ ID NO: 777; and SEQ ID NO: 779) of the heavy chain sequence of SEQ ID NO: 761 or the variable heavy chain sequence of SEQ ID NO: 762; and polynucleotides encoding the framework regions

(SEQ ID NO: 793; SEQ ID NO: 795; SEQ ID NO: 797; and SEQ ID NO: 799) of the light chain sequence of SEQ ID NO: 781 or the variable light chain sequence of SEQ ID NO: 782.

[1085] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab11.H, the polynucleotides encoding the full length Ab11.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 771 encoding the heavy chain sequence of SEQ ID NO: 761 and the polynucleotide SEQ ID NO: 791 encoding the light chain sequence of SEQ ID NO: 781.

[1086] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab11.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab11.H or Fab fragments thereof may be produced via expression of Ab11.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1087] Antibody Ab11A.H

[1088] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 801:

gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtgcctat
gacatcctctgggtccgtcaggctccagggaaggggctggagtccatcggaatgatgtatgatgatggtgacacatactacgctacttctgctaaag
gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
ggtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccctggcaccctcctccaag
agcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgacca
gcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccaga
cctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagaaagttgagcccaaatcttgtgacaaaactcacacatgcccaccg
tgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggacccctgaggtcaca
tgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgc
gggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggt
ctccaacaaagccctcccagccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatc
ccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgg
gcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggt

ggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 811).

[1089] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 802: gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggattcaccgtcagtgcctat gacatcctctgggtccgtcaggctccagggaaggggctggagtccatcggaatgatgtatgatgatggtgacacatactacgctacttctgctaaag gccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa ggtgtgagtaatatctggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 812).

[1090] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 810: gcctccaccaagggcccatcggtcttcccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga caagaaagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccc ccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttca actggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctca ccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctccaa agccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctgg tcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggactc cgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctct gcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 820).

[1091] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 821: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattggtagtagctt ggcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgaaggtagtagtagtagttact atggtattggtttcggcggaggaaccaaggtggaaatcaaacgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaa tctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactc ccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacaca aagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 831).

[1092] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 822:

gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattggtagtagctt ggcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctattctgcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgaaggtagtagtagttact atggtattggtttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 832).

[1093] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 830: acggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccag agaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcaccta cagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcc cgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 840).

[1094] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 814; SEQ ID NO: 816; and SEQ ID NO: 818, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 801 or the variable heavy chain sequence of SEQ ID NO: 802, and/or one or more of the polynucleotide sequences of SEQ ID NO: 834; SEQ ID NO: 836 and SEQ ID NO: 838, which correspond to the complementarity-determining regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 821 or the variable light chain sequence of SEQ ID NO: 822, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1095] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 813; SEQ ID NO: 815; SEQ ID NO: 817; and SEQ ID NO: 819, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 801 or the variable heavy chain sequence of SEQ ID NO: 802, and/or one or more of the polynucleotide sequences of SEQ ID NO: 833; SEQ ID NO: 835; SEQ ID NO: 837; and SEQ ID NO: 839, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 821 or the variable light chain sequence of SEQ ID NO: 822, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and

variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1096] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 811 encoding the heavy chain sequence of SEQ ID NO: 801; the polynucleotide SEQ ID NO: 812 encoding the variable heavy chain sequence of SEQ ID NO: 802; the polynucleotide SEQ ID NO: 831 encoding the light chain sequence of SEQ ID NO: 821; the polynucleotide SEQ ID NO: 832 encoding the variable light chain sequence of SEQ ID NO: 822; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 814; SEQ ID NO: 816; and SEQ ID NO: 818) of the heavy chain sequence of SEQ ID NO: 801 or the variable heavy chain sequence of SEQ ID NO: 802; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 834; SEQ ID NO: 836; and SEQ ID NO: 838) of the light chain sequence of SEQ ID NO: 821 or the variable light chain sequence of SEQ ID NO: 822; polynucleotides encoding the framework regions (SEQ ID NO: 813; SEQ ID NO: 815; SEQ ID NO: 817; and SEQ ID NO: 819) of the heavy chain sequence of SEQ ID NO: 801 or the variable heavy chain sequence of SEQ ID NO: 802; and polynucleotides encoding the framework regions (SEQ ID NO: 833; SEQ ID NO: 835; SEQ ID NO: 837; and SEQ ID NO: 839) of the light chain sequence of SEQ ID NO: 821 or the variable light chain sequence of SEQ ID NO: 822.

[1097] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab11A.H, the polynucleotides encoding the full length Ab11A.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 811 encoding the heavy chain sequence of SEQ ID NO: 801 and the polynucleotide SEQ ID NO: 831 encoding the light chain sequence of SEQ ID NO: 821.

[1098] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab11A.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab11A.H or Fab fragments thereof may be produced via expression of Ab11A.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1099] Antibody Ab12.H

[1100] In one embodiment, the invention is further directed to polynucleotides encoding antibody polypeptides having binding specificity to ACTH. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain sequence of SEQ ID NO: 841:
gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggatcctccctcagtgattatg
acatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatcatttatgatgatggtgacacatactacgctacttctgctaaagg
ccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaag
gtgtgagtaatatgtggggccaagggaccctcgtcaccgtctcgagcgcctccaccaagggcccatcggtcttcccccctggcaccctcctccaaga
gcacctctgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccag
cggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagac
ctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgt
gcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacat
gcgtggtggtggacgtgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgc
gggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggt
ctccaacaaagccctcccagcccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatc
ccgggaggagatgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgg
gcagccggagaacaactacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggt
ggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa
(SEQ ID NO: 851).

[1101] In another embodiment of the invention, the polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 842:
gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgcagcctctggatcctccctcagtgattatg
acatgatctgggtccgtcaggctccagggaaggggctggagtccatcggaatcatttatgatgatggtgacacatactacgctacttctgctaaagg
ccgattcaccatctccagagacaattccaagaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaag
gtgtgagtaatatgtggggccaagggaccctcgtcaccgtctcgagc (SEQ ID NO: 852).

[1102] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant heavy chain polypeptide sequence of SEQ ID NO: 850:
gcctccaccaagggcccatcggtcttcccccctggcaccctcctccaagagcacctctgggggcacagcggccctgggctgcctggtcaaggact
acttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctact
ccctcagcagcgtggtgaccgtgccctccagcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtgga
cgcgagagttgagcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttccc
cccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagttc
aactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctc

accgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccagcccccatcgagaaaaccatctcca aagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctgacctgcctg gtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactacaagaccacgcctcccgtgctggact ccgacggctccttcttcctctacagcaagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctc tgcacaaccactacacgcagaagagcctctccctgtctccgggtaaa (SEQ ID NO: 860).

[1103] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 861: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattggtagtagctt agcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctatgctgcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagtagtt atggtgttggtttcggcggaggaaccaaggtggaaatcaaacgtacggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaa tctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactc ccaggagagtgtcacagagcaggacagcaaggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacaca aagtctacgcctgcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 871).

[1104] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 862: gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgtcaggccagtcagagcattggtagtagctt agcctggtatcagcagaaaccaggaaaagcccctaagctcctgatctatgctgcatccactctggcatctggagtcccatcaaggttcagcggcagt ggatctggaacagaattcactctcaccatcagcagcctgcagcctgatgattttgcaacttactactgtcaaagctatgatggtagtagtagtagtt atggtgttggtttcggcggaggaaccaaggtggaaatcaaacgt (SEQ ID NO: 872).

[1105] In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the constant light chain polypeptide sequence of SEQ ID NO: 870: acggtggctgcaccatctgtcttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccag agaggccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagcaccta cagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatcagggcctgagctcgcc cgtcacaaagagcttcaacaggggagagtgt (SEQ ID NO: 880).

[1106] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 854; SEQ ID NO: 856; and SEQ ID NO: 858, which correspond to polynucleotides encoding the complementarity-determining regions (CDRs or hypervariable regions) of the heavy chain sequence of SEQ ID NO: 841 or the variable heavy chain sequence of SEQ ID NO: 842, and/or one or more of the polynucleotide sequences of SEQ ID NO: 874; SEQ ID NO: 876 and SEQ ID NO: 878, which correspond to the complementarity-determining

regions (CDRs or hypervariable regions) of the light chain sequence of SEQ ID NO: 861 or the variable light chain sequence of SEQ ID NO: 862, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of polynucleotides encoding one or more of the CDRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1107] In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 853; SEQ ID NO: 855; SEQ ID NO: 857; and SEQ ID NO: 859, which correspond to polynucleotides encoding the framework regions (FRs or constant regions) of the heavy chain sequence of SEQ ID NO: 841 or the variable heavy chain sequence of SEQ ID NO: 842, and/or one or more of the polynucleotide sequences of SEQ ID NO: 873; SEQ ID NO: 875; SEQ ID NO: 877; and SEQ ID NO: 879, which correspond to the framework regions (FRs or constant regions) of the light chain sequence of SEQ ID NO: 861 or the variable light chain sequence of SEQ ID NO: 862, or combinations of these polynucleotide sequences. In another embodiment of the invention, the polynucleotides encoding the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the FRs, the variable heavy chain and variable light chain sequences, and the heavy chain and light chain sequences set forth above, including all of them.

[1108] The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to ACTH comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 851 encoding the heavy chain sequence of SEQ ID NO: 841; the polynucleotide SEQ ID NO: 852 encoding the variable heavy chain sequence of SEQ ID NO: 842; the polynucleotide SEQ ID NO: 871 encoding the light chain sequence of SEQ ID NO: 861; the polynucleotide SEQ ID NO: 872 encoding the variable light chain sequence of SEQ ID NO: 862; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 854; SEQ ID NO: 856; and SEQ ID NO: 858) of the heavy chain sequence of SEQ ID NO: 841 or the variable heavy chain sequence of SEQ ID NO: 842; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 874; SEQ ID NO: 876; and SEQ ID NO: 878) of the light chain sequence of SEQ ID NO: 861 or the variable light chain sequence of SEQ ID NO: 862; polynucleotides encoding the framework regions (SEQ ID NO: 853; SEQ ID NO: 855; SEQ ID NO: 857; and SEQ ID NO: 859) of the heavy chain sequence of SEQ ID NO: 841 or the variable heavy chain sequence of SEQ ID NO: 842; and polynucleotides encoding the framework regions

(SEQ ID NO: 873; SEQ ID NO: 875; SEQ ID NO: 877; and SEQ ID NO: 879) of the light chain sequence of SEQ ID NO: 861 or the variable light chain sequence of SEQ ID NO: 862.

[1109] In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for ACTH. With respect to antibody Ab12.H, the polynucleotides encoding the full length Ab12.H antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 851 encoding the heavy chain sequence of SEQ ID NO: 841 and the polynucleotide SEQ ID NO: 871 encoding the light chain sequence of SEQ ID NO: 861.

[1110] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast Pichia. Suitable Pichia species include, but are not limited to, Pichia pastoris. In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab12.H following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-ACTH antibodies such as Ab12.H or Fab fragments thereof may be produced via expression of Ab12.H polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid Pichia) and other yeast strains. Suitable Pichia species include, but are not limited to, Pichia pastoris.

[1111] Host cells and vectors comprising said polynucleotides are also contemplated.

[1112] The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual complementarity-determining regions (CDRs, or hypervariable regions), as set forth herein, as well as host cells comprising said vector sequences. In one embodiment of the invention, the host cell is a yeast cell. In another embodiment of the invention, the yeast host cell belongs to the genus *Pichia*.

[1113] ***Exemplary Embodiments of the Subject Disclosure***

[1114] B-cell Screening and Isolation

[1115] The subject anti-ACTH antibodies and variants thereof, especially chimerized variants were obtained from clonal populations of B cells derived from rabbits which had been immunized with human ACTH. Such B cell screening and isolation methods have been previously described and are disclosed in US Provisional Application No. 61/791,755 filed March 15, 2013, and U.S. Ser. No. 14/217,594 filed March 18, 2014, which each of which is expressly incorporated by reference herein.

[1116] Methods of Humanizing Antibodies

[1117] In another embodiment, the present invention contemplates methods for humanizing antibody heavy and light chains. Methods for humanizing antibody heavy and light chains which may be applied to anti-ACTH antibodies are taught, for example, in U.S. patent application publication no.

US 2009/0022659 to Olson *et al.*, and in U.S. patent no. 7,935,340 to Garcia-Martinez *et al.*, the disclosures of each of which are herein incorporated by reference in their entireties.

[1118] Methods of Producing Antibodies and Fragments thereof

[1119] In another embodiment, the present invention contemplates methods for producing anti-ACTH antibodies and fragments thereof. Methods for producing anti-ACTH antibodies and fragments thereof secreted from polyploid, preferably diploid or tetraploid strains of mating competent yeast are taught, for example, in U.S. patent application publication no. US 2009/0022659 to Olson *et al.*, and in U.S. patent no. 7,935,340 to Garcia-Martinez *et al.*, the disclosures of each of which are herein incorporated by reference in their entireties. A preferred yeast for manufacture of antibodies is of the genus *Pichia*, and more preferably *Pichia pastoris*. However, antibodies according to the invention potentially may be made in other yeast such as other mating competent yeast of the Saccharomycetaceae family, which includes the genera *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*. Other types of yeast potentially useful for making antibody proteins according to the invention include *Yarrowia*; *Rhodosporidium*; *Candida*; *Hansenula*; *Filobasium*; *Sporidiobolus*; *Bullera*; *Leucosporidium* and *Filobasidella*.

[1120] Other methods of producing antibodies are well known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art (*See*, for example, U.S. Patent No. 4,816,567 to Cabilly *et al.*; Morrison et al., *PNAS. USA*, 81:8651-55 (1984); Neuberger, M.S. et al., *Nature*, 314:268-270 (1985); Boulianne, G.L. et al., *Nature*, 312:643-46 (1984), the disclosures of each of which are herein incorporated by reference in their entireties).

[1121] Likewise, other methods of producing humanized antibodies are now well known in the art (*See*, for example, U.S. Patent Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370 to Queen *et al*; U.S. Patent Nos. 5,225,539 and 6,548,640 to Winter; U.S. Patent Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter *et al*; U.S. Patent No. 6,632,927 to Adair; Jones, P.T. *et al*, *Nature*, 321:522-525 (1986); Reichmann, L., *et al*, *Nature*, 332:323-327 (1988); Verhoeyen, M, *et al*, *Science*, 239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

[1122] Antibody polypeptides of the invention having ACTH binding specificity may also be produced by constructing, using conventional techniques well known to those of ordinary skill in the art, an expression vector containing an operon and a DNA sequence encoding an antibody heavy chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

[1123] A second expression vector is produced using the same conventional means well known to those of ordinary skill in the art, said expression vector containing an operon and a DNA sequence

encoding an antibody light chain in which the DNA sequence encoding the CDRs required for antibody specificity is derived from a non-human cell source, preferably a rabbit B-cell source, while the DNA sequence encoding the remaining parts of the antibody chain is derived from a human cell source.

[1124] The expression vectors are transfected into a host cell by convention techniques well known to those of ordinary skill in the art to produce a transfected host cell, said transfected host cell cultured by conventional techniques well known to those of ordinary skill in the art to produce said antibody polypeptides.

[1125] The host cell may be co-transfected with the two expression vectors described above, the first expression vector containing DNA encoding an operon and a light chain-derived polypeptide and the second vector containing DNA encoding an operon and a heavy chain-derived polypeptide. The two vectors contain different selectable markers, but preferably achieve substantially equal expression of the heavy and light chain polypeptides. Alternatively, a single vector may be used, the vector including DNA encoding both the heavy and light chain polypeptides. The coding sequences for the heavy and light chains may comprise cDNA, genomic DNA, or both.

[1126] Host cells which potentially may be used to express the subject antibody polypeptides may include bacterial cells such as *E. coli*, or eukaryotic cells such as *P. pastoris*, other yeast cells, fungi, insect cells, mammalian cells, and plant cells. In one embodiment of the invention, a mammalian cell of a well-defined type may be for this purpose, such as a myeloma cell, a Chinese hamster ovary (CHO) cell line, a NSO cell line, or a HEK293 cell line.

[1127] The general methods by which the vectors may be constructed, transfection methods required to produce the host cell and culturing methods required to produce the antibody polypeptides from said host cells all include conventional techniques. Although preferably the cell line used to produce the antibody is a mammalian cell line, any other suitable cell line, such as a bacterial cell line such as an *E. coli*-derived bacterial strain, or a yeast cell line, may alternatively be used.

[1128] Similarly, once produced the antibody polypeptides may be purified according to standard procedures in the art, such as for example cross-flow filtration, ammonium sulphate precipitation, affinity column chromatography and the like.

[1129] The antibody polypeptides described herein may also be used for the design and synthesis of either peptide or non-peptide mimetics that would be useful for the same therapeutic applications as the antibody polypeptides of the invention. *See*, for example, Saragobi *et al*, *Science*, 253:792-795 (1991), the contents of which are herein incorporated by reference in its entirety.

[1130] Screening Assays

[1131] The invention also includes screening assays designed to assist in the identification of diseases and disorders associated with ACTH in subjects exhibiting symptoms of an ACTH associated disease or disorder.

[1132] In some embodiments, the antibody is used as a diagnostic tool. The antibody can be used to assay the amount of ACTH present in a sample and/or subject. As will be appreciated by one of skill in the art, such antibodies need not be neutralizing antibodies. In some embodiments, the diagnostic antibody is not a neutralizing antibody. In some embodiments, the diagnostic antibody binds to a different epitope than the neutralizing antibody binds to. In some embodiments, the two antibodies do not compete with one another.

[1133] In some embodiments, the antibodies disclosed herein are used or provided in an assay kit and/or method for the detection of ACTH in mammalian tissues or cells in order to screen/diagnose for a disease or disorder associated with changes in levels of ACTH. The kit comprises an antibody that binds ACTH and means for indicating the binding of the antibody with ACTH, if present, and optionally ACTH protein levels. Various means for indicating the presence of an antibody can be used. For example, fluorophores, other molecular probes, or enzymes can be linked to the antibody and the presence of the antibody can be observed in a variety of ways. The method for screening for such disorders can involve the use of the kit, or simply the use of one of the disclosed antibodies and the determination of whether the antibody binds to ACTH in a sample. As will be appreciated by one of skill in the art, high or elevated levels of ACTH will result in larger amounts of the antibody binding to ACTH in the sample. Thus, degree of antibody binding can be used to determine how much ACTH is in a sample. Subjects or samples with an amount of ACTH that is greater than a predetermined amount (e.g., an amount or range that a person without an ACTH-related disorder would have) can be characterized as having an ACTH-mediated disorder. In some embodiments, the antibody is administered to a subject taking a statin, in order to determine if the statin has affected the amount of ACTH in the subject.

[1134] The invention is also directed to a method of *in vivo* imaging which detects the presence of cells which express ACTH comprising administering a diagnostically effective amount of a diagnostic composition. Said *in vivo* imaging is useful for the detection or imaging of ACTH expressing cells or organs, for example, and can be useful as part of a planning regimen for the design of an effective treatment protocol.

[1135] The present invention further provides for a kit for detecting binding of an anti-ACTH antibody of the invention to ACTH. In particular, the kit may be used to detect the presence of an ACTH specifically reactive with an anti-ACTH antibody of the invention or an immunoreactive fragment thereof. The kit may also include an antibody bound to a substrate, a secondary antibody reactive with the antigen and a reagent for detecting a reaction of the secondary antibody with the antigen. Such a kit may be an ELISA kit and can comprise the substrate, primary and secondary antibodies when appropriate, and any other necessary reagents such as detectable moieties, enzyme substrates, and color reagents, for example as described herein. The diagnostic kit may also be in the form of an immunoblot kit. The diagnostic kit may also be in the form of a chemiluminescent kit

(Meso Scale Discovery, Gaithersburg, MD). The diagnostic kit may also be a lanthanide-based detection kit (PerkinElmer, San Jose, CA).

[1136] A skilled clinician would understand that a biological sample includes, but is not limited to, sera, plasma, urine, saliva, mucous, pleural fluid, synovial fluid and spinal fluid.

[1137] Methods of Ameliorating or Reducing Symptoms of, or Treating, or Preventing, Diseases and Disorders Associated with, ACTH

[1138] In another embodiment of the invention, anti-ACTH antibodies described herein, or fragments thereof, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with ACTH. As mentioned, these conditions include, by way of example, ACTH-driven hypercortisolism, acute coronary syndrome, acute heart failure, anxiety disorders, atherosclerosis, atrial fibrillation, cachexia, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), cardiac conditions, cardiac fibrosis, cardiovascular disorders, chronic renal failure, chronic stress syndrome, cognitive dysfunction, Alzheimer's disease, congestive heart failure, Conn's syndrome, coronary heart diseases, Cushing's Disease, Cushing's Syndrome, depression, diabetes, endothelial dysfunction, exercise intolerance, familial hyperaldosteronism, fibrosis, galactorrhea, heart failure, hyperaldosteronism, hypercortisolemia, hypertension, hyperinsulinemia, hypokalemia, impaired cardiac function, increased formation of collagen, inflammation, metabolic syndrome, muscle atrophy, conditions associated with muscle atrophy, myocardiac fibrosis, nephropathy, obesity, post-myocardial infarction, primary hyperaldosteronism, remodeling following hypertension, renal failure, restenosis, secondary hyperaldosteronism, sleep apnea, adrenal hyperplasia (such as congenital adrenal hyperplasia), stress related conditions, or syndrome X.

[1139] Anti-ACTH antibodies described herein, or fragments thereof, as well as combinations, can also be administered in a therapeutically or prophylactically effective amount to subjects in need of treatment or prevention of diseases and disorders associated with ACTH in the form of a pharmaceutical or diagnostic composition as described in greater detail below.

[1140] In another embodiment of the invention, anti-ACTH antibodies described herein, or fragments thereof, with or without a second agent, are useful for ameliorating or reducing the symptoms of, or treating, or preventing, disorders that relate to, involve, or can be influenced by varied ACTH, corticosterone, cortisol, and/or aldosterone levels. The anti-ACTH antibody may reduce plasma cortisol levels, but may not abolish plasma cortisol levels. The anti-ACTH antibody may reduce plasma corticosterone levels, but may not abolish plasma corticosterone levels. In some embodiments, the antibody or antibody fragment according to the invention is useful in reducing the risk of, symptoms of, treating, or preventing ACTH-driven hypercortisolism (Cushing's Disease and/or Cushing's Syndrome), obesity, diabetes, adrenal hyperplasia (such as congenital adrenal

hyperplasia), sleep disorders such as, e.g., sleep apnea, narcolepsy and insomnia, depression, anxiety disorders, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), muscle atrophy, hypertension, hyperinsulinemia, cognitive dysfunction, Alzheimer's disease, galactorrhea, stress related conditions, impaired cardiac function, exercise intolerance, heart failure and other cardiac conditions, metabolic syndrome, hyperaldosteronism including primary hyperaldosteronism (such as Conn's syndrome) secondary hyperaldosteronism, and familial hyperaldosteronism.

[1141] Administration

[1142] In one embodiment of the invention, the anti-ACTH antibodies described herein, or ACTH binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of between about 0.1 and 100.0 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-ACTH antibodies described herein, or ACTH binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-ACTH antibodies described herein, or ACTH binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a recipient subject with a frequency of once every twenty-six weeks or less, such as once every sixteen weeks or less, once every eight weeks or less, once every four weeks or less, once every two weeks or less, once every week or less, or once daily or less.

[1143] Fab fragments may be administered every two weeks or less, every week or less, once daily or less, multiple times per day, and/or every few hours. In one embodiment of the invention, a subject receives Fab fragments of 0.1 mg/kg to 40 mg/kg per day given in divided doses of 1 to 6 times a day, or in a sustained release form, effective to obtain desired results.

[1144] It is to be understood that the concentration of the antibody or Fab administered to a given subject may be greater or lower than the exemplary administration concentrations set forth above.

[1145] A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, L. S., Gilman, A., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). Pharmacology. Lippincott's illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). Principles of pharmacology: the pathophysiologic basis of drug therapy. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

[1146] In another embodiment of the invention, the anti-ACTH antibodies described herein, or ACTH binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject in a pharmaceutical formulation.

[1147] A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration *via* one or more of a number of routes, including but not limited to buccal, epicutaneous, epidural, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, rectally *via* an enema or suppository, subcutaneous, subdermal, transdermal, and transmucosal. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

[1148] In one embodiment of the invention, the anti-ACTH antibodies described herein, or ACTH binding fragments thereof, as well as combinations of said antibodies or antibody fragments, may be optionally administered in combination with one or more active agents. Such active agents include ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil (Provigil®). Additional exemplary active agents that may be administered in combination with the subject antibodies or fragments include without limitation thereto one or more of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-l mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors,

endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor (milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), or Zestril (lisinopril). Any suitable combination of these active agents is also contemplated.

[1149] A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or one or more fragments thereof. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington's Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

[1150] As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, or intramuscular administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active

compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[1151] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition. The proper fluidity can be maintained, for example, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[1152] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the alkaline polypeptide can be formulated in a time-release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[1153] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, injectables (including subcutaneous, intramuscular, intravenous, and intradermal), infusions, and combinations thereof.

[1154] Certain teachings related to humanization of rabbit-derived monoclonal antibodies and preferred sequence modifications to maintain antigen binding affinity were disclosed in International Application No. PCT/US2008/064421, corresponding to International Publication No. WO/2008/144757, entitled "Novel Rabbit Antibody Humanization Methods and Humanized Rabbit Antibodies", filed May 21, 2008, the disclosure of which is herein incorporated by reference in its entirety.

[1155] Certain teachings related to producing antibodies or fragments thereof using mating competent yeast and corresponding methods were disclosed in U.S. Patent application no. 11/429,053, filed May 8, 2006, (U.S. Patent Application Publication No. US2006/0270045), the disclosure of which is herein incorporated by reference in its entirety.

[1156] *Veterinary Uses of The Subject Antibodies*

[1157] The present disclosure additionally provides the use of the subject antibodies in non-human animals. The working examples herein demonstrate that the subject antibodies bind within a region of human ACTH that is conserved among animal species including dog, cat, and horse. A fragment of ACTH containing this conserved epitope sequence (ACTH 1-24) can activate ACTH receptors, and the subject antibodies are demonstrated herein to inhibit receptor activation by this fragment. Based on these and other results presented herein, it is expected that the antibodies of the invention will be therapeutically effective for antagonizing ACTH in vivo in these and other animal species. Thus, antibodies or antibody fragments comprising one or more, or all, of the CDRs of any one of the antibodies disclosed herein (e.g., Ab1-Ab7, Ab9-Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H) may be effective to treat a condition associated with ACTH in a non-human animal.

[1158] In exemplary embodiments, the disclosure provides a therapeutic method comprising administering an antibody or antibody fragment comprising one or more, or all, of the CDRs of any one of the anti-ACTH antibodies disclosed herein (e.g., Ab1-Ab7, Ab9-Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H) to a non-human animal in need thereof.

[1159] In exemplary embodiments, the disclosure provides a therapeutic composition comprising an antibody or antibody fragment comprising one or more, or all, of the CDRs of any one of the anti-ACTH antibodies disclosed herein (e.g., Ab1-Ab7, Ab9-Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H) which is adapted for administration to a non-human animal in need thereof.

[1160] In exemplary embodiments, the disclosure provides a comprising an antibody or antibody fragment comprising one or more, or all, of the CDRs of any one of the anti-ACTH antibodies disclosed herein (e.g., Ab1-Ab7, Ab9-Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H) for use in the treatment of a non-human animal in need thereof.

[1161] Said antibody or fragment may be modified to reduce the potential immune reaction of said animal. For example, said antibody may be a chimeric antibody comprising the variable light and/or variable heavy domain of any one of the anti-ACTH antibodies disclosed herein (e.g., Ab1-Ab7, Ab9-Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H,

Ab11A.H, and Ab12.H) in combination with a constant domain sequence of the respective animal species (such as dog, cat, or horse). Said antibody or fragment may comprise an antibody fragment, such as scFvs, Fab fragments, Fab' fragments, monovalent antibody fragments, and $F(ab')_2$ fragments. Said antibody or fragment may comprise a species-ized antibody (e.g., caninized, felinized, or equinized antibody for cats, dogs, or horses, respectively) produced by a process analogous to humanization, wherein one or more framework sequences or framework residues are replaced by framework sequences or residues contained within endogenous framework sequences of antibodies of the respective species.

[1162] Said animal species may be a species in which endogenous ACTH is conserved, e.g., having the same sequence as human ACTH, or having up to one, two, three, four, or five sequence differences from human ACTH or from human ACTH 1-24. For example, the ACTH of said species may have one or more, or all, of the epitope binding residues identified in the examples herein that are the same as the residues in human ACTH, or having conservative substitutions relative to the corresponding residues in human ACTH. Preferably the administered anti-ACTH antibody is able to bind to ACTH of said animal species and antagonize activation of an ACTH receptor in said animal species.

[1163] ***Additional Exemplary Embodiments of the Invention***

[1164] Additional exemplary embodiments of the invention are set forth in the following clauses.

[1165] Clause 1A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment that specifically binds to a linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1166] Clause 2A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment of Clause 1A, which specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as Ab2 or Ab3.

[1167] Clause 3A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment of Clause 1A, which specifically binds to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1168] Clause 4A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment of Clause 1A, which specifically binds to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab2 or Ab3.

[1169] Clause 5A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment of Clause 1A, wherein said epitope(s) is identified using a binding assay that detects the binding of said anti-human ACTH antibody or antibody fragment to one or more peptides in a library of overlapping linear peptide fragments that span the full length of human ACTH.

[1170] Clause 6A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment of Clause 1A, wherein said epitope is identified using alanine scanning.

[1171] Clause 7A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment that contains at least 2 complementarity determining regions (CDRs) of an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1172] Clause 8A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to Clause 7A, which contains at least 3 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1173] Clause 9A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to Clause 7A, which contains at least 4 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1174] Clause 10A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to Clause 7A, which contains at least 5 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1175] Clause 11A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to Clause 7A, which contains all 6 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group

consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1176] Clause 12A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1177] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:4; a CDR2 sequence consisting of SEQ ID NO:6; and a CDR3 sequence consisting of SEQ ID NO:8; and/or

[1178] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:24; a CDR2 sequence consisting of SEQ ID NO:26; and a CDR3 sequence consisting of SEQ ID NO:28.

[1179] Clause 13A. A anti-human ACTH antibody or antibody fragment according to Clause 12A, which comprises:

[1180] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 2 and/or

[1181] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:22.

[1182] Clause 14A. An anti-human ACTH antibody or antibody fragment according to Clause 12A, which comprises:

[1183] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:2, and/or

[1184] (b) a variable light chain having the amino acid sequence of SEQ ID NO:22.

[1185] Clause 15A. An anti-human ACTH antibody or antibody fragment according to Clause 12A, which comprises:

[1186] (a) a heavy chain having the amino acid sequence of SEQ ID NO:1, and/or

[1187] (b) a light chain having the amino acid sequence of SEQ ID NO:21.

[1188] Clause 16A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1189] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:44; a CDR2 sequence consisting of SEQ ID NO:46; and a CDR3 sequence consisting of SEQ ID NO:48; and/or

[1190] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:64; a CDR2 sequence consisting of SEQ ID NO:66; and a CDR3 sequence consisting of SEQ ID NO:68.

[1191] Clause 17A. An anti-human ACTH antibody or antibody fragment according to Clause 16A, which comprises:

[1192] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:42, and/or

[1193] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:62.

[1194] Clause 18A. An anti-human ACTH antibody or antibody fragment according to Clause 16A, which comprises:

[1195] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:42, and/or

[1196] (b) a variable light chain having the amino acid sequence of SEQ ID NO:62.

[1197] Clause 19A. An anti-human ACTH antibody or antibody fragment according to Clause 16A, which comprises:

[1198] (a) a heavy chain having the amino acid sequence of SEQ ID NO:41, and/or

[1199] (b) a light chain having the amino acid sequence of SEQ ID NO:61.

[1200] Clause 20A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1201] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:84; a CDR2 sequence consisting of SEQ ID NO:86; and a CDR3 sequence consisting of SEQ ID NO:88; and/or

[1202] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:104; a CDR2 sequence consisting of SEQ ID NO:106; and a CDR3 sequence consisting of SEQ ID NO:108.

[1203] Clause 21A. An anti-human ACTH antibody or antibody fragment according to Clause 20A, which comprises:

[1204] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:82 and/or

[1205] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:102.

[1206] Clause 22A. An anti-human ACTH antibody or antibody fragment according to Clause 20A, which comprises:

[1207] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:82, and/or

[1208] (b) a variable light chain having the amino acid sequence of SEQ ID NO:102.

[1209] Clause 23A. An anti-human ACTH antibody or antibody fragment according to Clause 20A, which comprises:

[1210] (a) a heavy chain having the amino acid sequence of SEQ ID NO:81, and/or

[1211] (b) a light chain having the amino acid sequence of SEQ ID NO:101.

[1212] Clause 24A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1213] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:124; a CDR2 sequence consisting of SEQ ID NO:126; and a CDR3 sequence consisting of SEQ ID NO:128; and/or

[1214] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:144; a CDR2 sequence consisting of SEQ ID NO:146; and a CDR3 sequence consisting of SEQ ID NO:148.

[1215] Clause 25A. An anti-human ACTH antibody or antibody fragment according to Clause 24A, which comprises:

[1216] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:122 and/or

[1217] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:142.

[1218] Clause 26A. An anti-human ACTH antibody or antibody fragment according to Clause 24A, which comprises:

[1219] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:122, and/or

[1220] (b) a variable light chain having the amino acid sequence of SEQ ID NO:142.

[1221] Clause 27A. An anti-human ACTH antibody or antibody fragment according to Clause 24A, which comprises:

[1222] (a) a heavy chain having the amino acid sequence of SEQ ID NO:121, and/or

[1223] (b) a light chain having the amino acid sequence of SEQ ID NO:141.

[1224] Clause 28A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1225] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:164; a CDR2 sequence consisting of SEQ ID NO:166; and a CDR3 sequence consisting of SEQ ID NO:168; and/or

[1226] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:184; a CDR2 sequence consisting of SEQ ID NO:186; and a CDR3 sequence consisting of SEQ ID NO:188.

[1227] Clause 29A. An anti-human ACTH antibody or antibody fragment according to Clause 28A, which comprises:

[1228] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:162, and/or

[1229] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:182.

[1230] Clause 30A. An anti-human ACTH antibody or antibody fragment according to Clause 28A, which comprises:

[1231] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:162, and/or

[1232] (b) a variable light chain having the amino acid sequence of SEQ ID NO:182.

[1233] Clause 31A. An anti-human ACTH antibody or antibody fragment according to Clause 28A, which comprises:

[1234] (a) a heavy chain having the amino acid sequence of SEQ ID NO:161, and/or

[1235] (b) a light chain having the amino acid sequence of SEQ ID NO:181.

[1236] Clause 32A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1237] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:204; a CDR2 sequence consisting of SEQ ID NO:206; and a CDR3 sequence consisting of SEQ ID NO:208; and/or

[1238] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:224; a CDR2 sequence consisting of SEQ ID NO:226; and a CDR3 sequence consisting of SEQ ID NO:228.

[1239] Clause 33A. An anti-human ACTH antibody or antibody fragment according to Clause 32A, which comprises:

[1240] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:202 and/or

[1241] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:222.

[1242] Clause 34A. An anti-human ACTH antibody or antibody fragment according to Clause 32A, which comprises:

[1243] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:202, and/or

[1244] (b) a variable light chain having the amino acid sequence of SEQ ID NO:223.

[1245] Clause 35A. An anti-human ACTH antibody or antibody fragment according to Clause 32A, which comprises:

[1246] (a) a heavy chain having the amino acid sequence of SEQ ID NO:201, and/or

[1247] (b) a light chain having the amino acid sequence of SEQ ID NO:221.

[1248] Clause 36A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1249] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:244; a CDR2 sequence consisting of SEQ ID NO:246; and a CDR3 sequence consisting of SEQ ID NO:248; and/or

[1250] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:264; a CDR2 sequence consisting of SEQ ID NO:266; and a CDR3 sequence consisting of SEQ ID NO:268.

[1251] Clause 37A. An anti-human ACTH antibody or antibody fragment according to Clause 36A, which comprises:

[1252] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:242 and/or

[1253] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:262.

[1254] Clause 38A. An anti-human ACTH antibody or antibody fragment according to Clause 36A, which comprises:

[1255] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:242, and/or

[1256] (b) a variable light chain having the amino acid sequence of SEQ ID NO:262.

[1257] Clause 39A. An anti-human ACTH antibody or antibody fragment according to Clause 36A, which comprises:

[1258] (a) a heavy chain having the amino acid sequence of SEQ ID NO:241, and/or

[1259] (b) a light chain having the amino acid sequence of SEQ ID NO:261.

[1260] Clause 40A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1261] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:284; a CDR2 sequence consisting of SEQ ID NO:286; and a CDR3 sequence consisting of SEQ ID NO:288; and/or

[1262] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:304; a CDR2 sequence consisting of SEQ ID NO:306; and a CDR3 sequence consisting of SEQ ID NO:308.

[1263] Clause 41A. An anti-human ACTH antibody or antibody fragment according to Clause 40A, which comprises:

[1264] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:282, and/or

[1265] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:302.

[1266] Clause 42A. An anti-human ACTH antibody or antibody fragment according to Clause 40A, which comprises:

[1267] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:282, and/or

[1268] (b) a variable light chain having the amino acid sequence of SEQ ID NO:302.

[1269] Clause 43A. An anti-human ACTH antibody or antibody fragment according to Clause 40A, which comprises:

[1270] (a) a heavy chain having the amino acid sequence of SEQ ID NO:281, and/or

[1271] (b) a light chain having the amino acid sequence of SEQ ID NO:301.

[1272] Clause 40.1A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1273] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:324; a CDR2 sequence consisting of SEQ ID NO:326; and a CDR3 sequence consisting of SEQ ID NO:328; and/or

[1274] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:344; a CDR2 sequence consisting of SEQ ID NO:346; and a CDR3 sequence consisting of SEQ ID NO:348.

[1275] Clause 41.1A. An anti-human ACTH antibody or antibody fragment according to Clause 40.1A, which comprises:

[1276] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:322, and/or

[1277] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:342.

[1278] Clause 42.1A. An anti-human ACTH antibody or antibody fragment according to Clause 40.1A, which comprises:

[1279] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:322, and/or

[1280] (b) a variable light chain having the amino acid sequence of SEQ ID NO:342.

[1281] Clause 43.1A. An anti-human ACTH antibody or antibody fragment according to Clause 40.1A, which comprises:

[1282] (a) a heavy chain having the amino acid sequence of SEQ ID NO:321, and/or

[1283] (b) a light chain having the amino acid sequence of SEQ ID NO:341.

[1284] Clause 40.2A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1285] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:364; a CDR2 sequence consisting of SEQ ID NO:366; and a CDR3 sequence consisting of SEQ ID NO:368; and/or

[1286] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:384; a CDR2 sequence consisting of SEQ ID NO:386; and a CDR3 sequence consisting of SEQ ID NO:388.

[1287] Clause 41.2A. An anti-human ACTH antibody or antibody fragment according to Clause 40.2A, which comprises:

[1288] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:362, and/or

[1289] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:382.

[1290] Clause 42.2A. An anti-human ACTH antibody or antibody fragment according to Clause 40.2A, which comprises:

[1291] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:362, and/or

[1292] (b) a variable light chain having the amino acid sequence of SEQ ID NO:382.

[1293] Clause 43.2A. An anti-human ACTH antibody or antibody fragment according to Clause 40.2A, which comprises:

[1294] (a) a heavy chain having the amino acid sequence of SEQ ID NO:361, and/or

[1295] (b) a light chain having the amino acid sequence of SEQ ID NO:381.

[1296] Clause 40.3A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1297] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:404; a CDR2 sequence consisting of SEQ ID NO:406; and a CDR3 sequence consisting of SEQ ID NO:408; and/or

[1298] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:424; a CDR2 sequence consisting of SEQ ID NO:426; and a CDR3 sequence consisting of SEQ ID NO:428.

[1299] Clause 41.3A. An anti-human ACTH antibody or antibody fragment according to Clause 40.3A, which comprises:

[1300] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:402, and/or

[1301] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:422.

[1302] Clause 42.3A. An anti-human ACTH antibody or antibody fragment according to Clause 40.3A, which comprises:

[1303] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:402, and/or

[1304] (b) a variable light chain having the amino acid sequence of SEQ ID NO:422.

[1305] Clause 43.3A. An anti-human ACTH antibody or antibody fragment according to Clause 40.3A, which comprises:

[1306] (a) a heavy chain having the amino acid sequence of SEQ ID NO:401, and/or

[1307] (b) a light chain having the amino acid sequence of SEQ ID NO:421.

[1308] Clause 40.4A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1309] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:444; a CDR2 sequence consisting of SEQ ID NO:446; and a CDR3 sequence consisting of SEQ ID NO:448; and/or

[1310] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:464; a CDR2 sequence consisting of SEQ ID NO:466; and a CDR3 sequence consisting of SEQ ID NO:468.

[1311] Clause 41.4A. An anti-human ACTH antibody or antibody fragment according to Clause 40.4A, which comprises:

[1312] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:442, and/or

[1313] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:462.

[1314] Clause 42.4A. An anti-human ACTH antibody or antibody fragment according to Clause 40.4A, which comprises:

[1315] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:442, and/or

[1316] (b) a variable light chain having the amino acid sequence of SEQ ID NO:462.

[1317] Clause 43.4A. An anti-human ACTH antibody or antibody fragment according to Clause 40.4A, which comprises:

[1318] (a) a heavy chain having the amino acid sequence of SEQ ID NO:441, and/or

[1319] (b) a light chain having the amino acid sequence of SEQ ID NO:461.

[1320] Clause 40.5A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1321] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:484; a CDR2 sequence consisting of SEQ ID NO:486; and a CDR3 sequence consisting of SEQ ID NO:488; and/or

[1322] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:504; a CDR2 sequence consisting of SEQ ID NO:506; and a CDR3 sequence consisting of SEQ ID NO:508.

[1323] Clause 41.5A. An anti-human ACTH antibody or antibody fragment according to Clause 40.5A, which comprises:

[1324] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:482, and/or

[1325] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:502.

[1326] Clause 42.5A. An anti-human ACTH antibody or antibody fragment according to Clause 40.5A, which comprises:

[1327] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:482, and/or

[1328] (b) a variable light chain having the amino acid sequence of SEQ ID NO:502.

[1329] Clause 43.5A. An anti-human ACTH antibody or antibody fragment according to Clause 40.5A, which comprises:

[1330] (a) a heavy chain having the amino acid sequence of SEQ ID NO:481, and/or

[1331] (b) a light chain having the amino acid sequence of SEQ ID NO:501.

[1332] Clause 40.6A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1333] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:524; a CDR2 sequence consisting of SEQ ID NO:526; and a CDR3 sequence consisting of SEQ ID NO:528; and/or

[1334] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:544; a CDR2 sequence consisting of SEQ ID NO:546; and a CDR3 sequence consisting of SEQ ID NO:548.

[1335] Clause 41.6A. An anti-human ACTH antibody or antibody fragment according to Clause 40.6A, which comprises:

[1336] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:522, and/or

[1337] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:542.

[1338] Clause 42.6A. An anti-human ACTH antibody or antibody fragment according to Clause 40.6A, which comprises:

[1339] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:522, and/or

[1340] (b) a variable light chain having the amino acid sequence of SEQ ID NO:542.

[1341] Clause 43.6A. An anti-human ACTH antibody or antibody fragment according to Clause 40.6A, which comprises:

[1342] (a) a heavy chain having the amino acid sequence of SEQ ID NO:521, and/or

[1343] (b) a light chain having the amino acid sequence of SEQ ID NO:541.

[1344] Clause 40.7A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1345] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:564; a CDR2 sequence consisting of SEQ ID NO:566; and a CDR3 sequence consisting of SEQ ID NO:568; and/or

[1346] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:584; a CDR2 sequence consisting of SEQ ID NO:586; and a CDR3 sequence consisting of SEQ ID NO:588.

[1347] Clause 41.7A. An anti-human ACTH antibody or antibody fragment according to Clause 40.7A, which comprises:

[1348] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:562, and/or

[1349] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:582.

[1350] Clause 42.7A. An anti-human ACTH antibody or antibody fragment according to Clause 40.7A, which comprises:

[1351] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:562, and/or

[1352] (b) a variable light chain having the amino acid sequence of SEQ ID NO:582.

[1353] Clause 43.7A. An anti-human ACTH antibody or antibody fragment according to Clause 40.7A, which comprises:

[1354] (a) a heavy chain having the amino acid sequence of SEQ ID NO:561, and/or

[1355] (b) a light chain having the amino acid sequence of SEQ ID NO:581.

[1356] Clause 40.8A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1357] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:604; a CDR2 sequence consisting of SEQ ID NO:606; and a CDR3 sequence consisting of SEQ ID NO:608; and/or

[1358] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:624; a CDR2 sequence consisting of SEQ ID NO:626; and a CDR3 sequence consisting of SEQ ID NO:628.

[1359] Clause 41.8A. An anti-human ACTH antibody or antibody fragment according to Clause 40.8A, which comprises:

[1360] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:602, and/or

[1361] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:622.

[1362] Clause 42.8A. An anti-human ACTH antibody or antibody fragment according to Clause 40.8A, which comprises:

[1363] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:602, and/or

[1364] (b) a variable light chain having the amino acid sequence of SEQ ID NO:622.

[1365] Clause 43.8A. An anti-human ACTH antibody or antibody fragment according to Clause 40.8A, which comprises:

[1366] (a) a heavy chain having the amino acid sequence of SEQ ID NO:601, and/or

[1367] (b) a light chain having the amino acid sequence of SEQ ID NO:621.

[1368] Clause 40.9A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1369] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:644; a CDR2 sequence consisting of SEQ ID NO:646; and a CDR3 sequence consisting of SEQ ID NO:648; and/or

[1370] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:664; a CDR2 sequence consisting of SEQ ID NO:666; and a CDR3 sequence consisting of SEQ ID NO:668.

[1371] Clause 41.9A. An anti-human ACTH antibody or antibody fragment according to Clause 40.9A, which comprises:

[1372] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:642, and/or

[1373] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:662.

[1374] Clause 42.9A. An anti-human ACTH antibody or antibody fragment according to Clause 40.9A, which comprises:

[1375] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:642, and/or

[1376] (b) a variable light chain having the amino acid sequence of SEQ ID NO:662.

[1377] Clause 43.9A. An anti-human ACTH antibody or antibody fragment according to Clause 40.9A, which comprises:

[1378] (a) a heavy chain having the amino acid sequence of SEQ ID NO:641, and/or

[1379] (b) a light chain having the amino acid sequence of SEQ ID NO:661.

[1380] Clause 40.10A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1381] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:684; a CDR2 sequence consisting of SEQ ID NO:686; and a CDR3 sequence consisting of SEQ ID NO:688; and/or

[1382] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:704; a CDR2 sequence consisting of SEQ ID NO:706; and a CDR3 sequence consisting of SEQ ID NO:708.

[1383] Clause 41.10A. An anti-human ACTH antibody or antibody fragment according to Clause 40.10A, which comprises:

[1384] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:682, and/or

[1385] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:702.

[1386] Clause 42.10A. An anti-human ACTH antibody or antibody fragment according to Clause 40.10A, which comprises:

[1387] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:682, and/or

[1388] (b) a variable light chain having the amino acid sequence of SEQ ID NO:702.

[1389] Clause 43.10A. An anti-human ACTH antibody or antibody fragment according to Clause 40.10A, which comprises:

[1390] (a) a heavy chain having the amino acid sequence of SEQ ID NO:681, and/or

[1391] (b) a light chain having the amino acid sequence of SEQ ID NO:701.

[1392] Clause 40.11A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1393] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:724; a CDR2 sequence consisting of SEQ ID NO:726; and a CDR3 sequence consisting of SEQ ID NO:728; and/or

[1394] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:744; a CDR2 sequence consisting of SEQ ID NO:746; and a CDR3 sequence consisting of SEQ ID NO:748.

[1395] Clause 41.11A. An anti-human ACTH antibody or antibody fragment according to Clause 40.11A, which comprises:

[1396] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:722, and/or

[1397] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:742.

[1398] Clause 42.11A. An anti-human ACTH antibody or antibody fragment according to Clause 40.11A, which comprises:

[1399] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:722, and/or

[1400] (b) a variable light chain having the amino acid sequence of SEQ ID NO:742.

[1401] Clause 43.11A. An anti-human ACTH antibody or antibody fragment according to Clause 40.11A, which comprises:

[1402] (a) a heavy chain having the amino acid sequence of SEQ ID NO:721, and/or

[1403] (b) a light chain having the amino acid sequence of SEQ ID NO:741.

[1404] Clause 40.12A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1405] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:764; a CDR2 sequence consisting of SEQ ID NO:766; and a CDR3 sequence consisting of SEQ ID NO:768; and/or

[1406] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:784; a CDR2 sequence consisting of SEQ ID NO:786; and a CDR3 sequence consisting of SEQ ID NO:788.

[1407] Clause 41.12A. An anti-human ACTH antibody or antibody fragment according to Clause 40.12A, which comprises:

[1408] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:762, and/or

[1409] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:782.

[1410] Clause 42.12A. An anti-human ACTH antibody or antibody fragment according to Clause 40.12A, which comprises:

[1411] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:762, and/or

[1412] (b) a variable light chain having the amino acid sequence of SEQ ID NO:782.

[1413] Clause 43.12A. An anti-human ACTH antibody or antibody fragment according to Clause 40.12A, which comprises:

[1414] (a) a heavy chain having the amino acid sequence of SEQ ID NO:761, and/or

[1415] (b) a light chain having the amino acid sequence of SEQ ID NO:781.

[1416] Clause 40.13A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1417] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:804; a CDR2 sequence consisting of SEQ ID NO:806; and a CDR3 sequence consisting of SEQ ID NO:808; and/or

[1418] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:824; a CDR2 sequence consisting of SEQ ID NO:826; and a CDR3 sequence consisting of SEQ ID NO:828.

[1419] Clause 41.13A. An anti-human ACTH antibody or antibody fragment according to Clause 40.13A, which comprises:

[1420] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:802, and/or

[1421] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:822.

[1422] Clause 42.13A. An anti-human ACTH antibody or antibody fragment according to Clause 40.13A, which comprises:

[1423] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:802, and/or

[1424] (b) a variable light chain having the amino acid sequence of SEQ ID NO:822.

[1425] Clause 43.13A. An anti-human ACTH antibody or antibody fragment according to Clause 40.13A, which comprises:

[1426] (a) a heavy chain having the amino acid sequence of SEQ ID NO:801, and/or

[1427] (b) a light chain having the amino acid sequence of SEQ ID NO:821.

[1428] Clause 40.14A. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-11A, which comprises:

[1429] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:844; a CDR2 sequence consisting of SEQ ID NO:846; and a CDR3 sequence consisting of SEQ ID NO:848; and/or

[1430] (b) a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:864; a CDR2 sequence consisting of SEQ ID NO:866; and a CDR3 sequence consisting of SEQ ID NO:868.

[1431] Clause 41.14A. An anti-human ACTH antibody or antibody fragment according to Clause 40.14A, which comprises:

[1432] (a) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:842, and/or

[1433] (b) a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:862.

[1434] Clause 42.14A. An anti-human ACTH antibody or antibody fragment according to Clause 40.14A, which comprises:

[1435] (a) a variable heavy chain having the amino acid sequence of SEQ ID NO:842, and/or

[1436] (b) a variable light chain having the amino acid sequence of SEQ ID NO:862.

[1437] Clause 43.14A. An anti-human ACTH antibody or antibody fragment according to Clause 40.14A, which comprises:

[1438] (a) a heavy chain having the amino acid sequence of SEQ ID NO:841, and/or

[1439] (b) a light chain having the amino acid sequence of SEQ ID NO:861.

[1440] Clause 44A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-43.14A, wherein the antibody or antibody fragment is selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR, Fab fragments, Fab' fragments, MetMab like antibodies, monovalent antibody fragments, and $F(ab')_2$ fragments.

[1441] Clause 45A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-44A, wherein the antibody or antibody fragment substantially or entirely lacks N-glycosylation and/or O-glycosylation.

[1442] Clause 46A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-45A, wherein the antibody or antibody fragment comprises a human constant domain, optionally, the heavy chain constant domain polypeptide of SEQ ID NO: 886, 887, or 888.

[1443] Clause 47A. The anti-human ACTH antibody or antibody fragment of Clause 46A, wherein the antibody is an IgG1, IgG2, IgG3, or IgG4 antibody.

[1444] Clause 48A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-47A, wherein the antibody or antibody fragment comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation.

[1445] Clause 49A. The anti-human ACTH antibody or antibody fragment of Clause 48A, wherein the Fc region contains one or more mutations that alters or eliminates N- and/or O-glycosylation.

[1446] Clause 50A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-49A, wherein the antibody or antibody fragment is a humanized antibody or antibody fragment.

[1447] Clause 51A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-50A, wherein the antibody or antibody fragment binds to ACTH with a binding affinity (K_D) of less than or equal to $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$

M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M, e.g., as determined by surface plasmon resonance (e.g., BIAcore®) at 25° or 37°C.

[1448] Clause 52A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-51A, wherein the antibody or antibody fragment binds to ACTH with a binding affinity (K_D) of less than or equal to $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M.

[1449] Clause 53A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-52A, which binds to ACTH with an off-rate (k_d) of less than or equal to $5x10^{-4}$ s^{-1}, 10^{-4} s^{-1}, $5x10^{-5}$ s^{-1}, or 10^{-5} s^{-1}.

[1450] Clause 54A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-53A, wherein the antibody or antibody fragment is directly or indirectly attached to a detectable label or therapeutic agent.

[1451] Clause 55A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-54A, which when administered to a human subject inhibits or neutralizes at least one biological effect elicited by ACTH.

[1452] Clause 56A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-55A, which neutralizes or inhibits ACTH activation of MC2R.

[1453] Clause 57A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-55A, which neutralizes or inhibits ACTH activation of at least one of MC1R, MC2R, MC3R, MC4R and MC5R or any combination thereof.

[1454] Clause 58A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-55A, which neutralizes or inhibits ACTH activation of each of MC2R, MC3R and MC4R.

[1455] Clause 59A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-55A, which inhibits ACTH-induced cortisol, corticosterone and/or aldosterone secretion, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1456] Clause 60A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-55A, which when administered to a human subject reduces plasma cortisol, aldosterone and/or corticosterone levels, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1457] Clause 61A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-60A, wherein the antibody or antibody fragment is capable of inhibiting the binding of ACTH to a MCR.

[1458] Clause 62A. The anti-human ACTH antibody or antibody fragment of Clause 61A, wherein the MCR is at least one of MC1R, MC2R, MC3R, MC4R and MC5R; at least one of MC2R,

MC3R, and MC4R; each of MC2R, MC3R, and MC4R; or each of MC1R, MC2R, MC3R, MC4R and MC5R.

[1459] Clause 63A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-62A, wherein the antibody or antibody fragment binds to ACTH with a K_D that is less than about 100 nM.

[1460] Clause 64A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-62A, which binds to ACTH with a K_D that is less than about 100 pM.

[1461] Clause 65A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-62A, which binds to ACTH with a K_D that is less than about 50 pM.

[1462] Clause 66A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-62A, which binds to ACTH with a K_D that is less than about 25 pM.

[1463] Clause 67A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-62A, which binds to ACTH with a K_D that is between about 10 pM and about 100 pM.

[1464] Clause 68A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-62A, which binds to ACTH with a K_D that is less than about 40 nM.

[1465] Clause 69A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-68A, which has stronger affinity for $ACTH_{1-39}$ as compared to alpha-MSH or CLIP and/or does not bind to alpha-MSH.

[1466] Clause 70A. The anti-human ACTH antibody or antibody fragment of Clause 69A, wherein the affinity of said antibody or antibody fragment to $ACTH_{1-39}$ is at least 10-fold, 100-fold, 1000-fold or more stronger than the affinity of said antibody or antibody fragment to alpha-MSH or CLIP (i.e., the K_D for ACTH is numerically lower than the K_D for alpha-MSH or CLIP by at least 10-fold, 100-fold, 1000-fold or more).

[1467] Clause 71A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-70A, wherein the antibody or antibody fragment is attached to at least one effector moiety.

[1468] Clause 72A. The anti-human ACTH antibody or antibody fragment of Clause 71A, wherein effector moiety comprises a chemical linker.

[1469] Clause 73A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-72A, wherein the antibody or antibody fragment is attached to one or more detectable moieties.

[1470] Clause 74A. The anti-human ACTH antibody or antibody fragment of Clause 73A, wherein detectable moiety comprises a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixtures thereof.

[1471] Clause 75A. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1A-74A, wherein the antibody or antibody fragment is attached to one or more functional moieties.

[1472] Clause 76A. An anti-idiotypic antibody produced against an anti-human ACTH antibody or antibody fragment according to any one of Clauses 1A-75A, which optionally, neutralizes one or more biological effects of the anti-human ACTH antibody to which it binds.

[1473] Clause 77A. A method of using the anti-idiotypic antibody of Clause 76A or another antibody that specifically binds said anti-human ACTH antibody to monitor the *in vivo* levels of said anti-ACTH antibody or antibody fragment in a subject or to neutralize said anti-ACTH antibody in a subject being administered said anti-ACTH antibody or antibody fragment or a method of using the anti-idiotypic antibody of Clause 76A or another antibody that specifically binds said anti-human ACTH antibody to neutralize the *in vivo* effects of said antibody in a subject in need thereof.

[1474] Clause 78A. A composition suitable for therapeutic, prophylactic, or a diagnostic use comprising a therapeutically, prophylactically or diagnostically effective amount of at least one anti-human ACTH antibody or antibody fragment or anti-idiotypic antibody according to any one of Clauses 1A-76A.

[1475] Clause 79A. The composition of Clause 78A, which is suitable for subcutaneous administration.

[1476] Clause 80A. The composition of Clause 78A, which is suitable for intravenous administration.

[1477] Clause 81A. The composition of Clause 78A, which is lyophilized.

[1478] Clause 82A. The composition of any one of Clauses 78A-81A, further comprising a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, or mixture thereof.

[1479] Clause 83A. The composition of any one of Clauses 78A-82A, further comprising another active agent.

[1480] Clause 84A. The composition of Clause 83A, wherein the other active agent is selected from the group consisting of ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil (Provigil®), or wherein the other active agent is selected from the group consisting of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-l mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide

dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor (milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), and Zestril (lisinopril).

[1481] Clause 85A. The composition of any one of Clauses 79A-84A, which is lyophilized, stabilized and/or formulated for administration by injection.

[1482] Clause 86A. An isolated nucleic acid sequence or nucleic acid sequences encoding an anti-human ACTH antibody or antibody fragment or anti-idiotypic antibody according to any one of Clauses 1A-76A.

[1483] Clause 87A. A vector or vectors containing the isolated nucleic acid sequence or sequences of Clause 86A.

[1484] Clause 88A. A host cell comprising the isolated nucleic acid sequence or sequences of Clause 87A or the vector or vectors of Clause 87A.

[1485] Clause 89A. The host cell of Clause 88A, which is a mammalian, bacterial, fungal, yeast, avian or insect cell.

[1486] Clause 90A. The host cell of Clause 89A, which is a filamentous fungi or a yeast.

[1487] Clause 91A. The host cell of Clause 90A, wherein the yeast is selected from the from the following genera: *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*.

[1488] Clause 92A. The host cell of Clause 91A, which is the yeast genus is *Pichia*.

[1489] Clause 93A. The host cell of Clause 92A, wherein the species of *Pichia* is selected from *Pichia pastoris*, *Pichia methanolica* and *Hansenula polymorpha* (*Pichia angusta*).

[1490] Clause 94A. A method of expressing an anti-human ACTH antibody or antibody fragment comprising culturing the host cell of any one of Clauses 89A-93A under conditions that provide for expression of said antibody or antibody fragment.

[1491] Clause 95A. The method of Clause 94A, wherein the host cell is a polyploid yeast culture that stably expresses and secretes into the culture medium at least 10-25 mg/liter of said antibody or antibody fragment.

[1492] Clause 96A. The method of Clause 95A, wherein said polyploid yeast is made by a method that comprises:

[1493] (i) introducing at least one expression vector containing one or more heterologous polynucleotides encoding said antibody operably linked to a promoter and a signal sequence into a haploid yeast cell;

[1494] (ii) producing by mating or spheroplast fusion a polyploid yeast from said first and/or second haploid yeast cell;

[1495] (iii) selecting polyploid yeast cells that stably express said antibody; and

[1496] (iv) producing stable polyploid yeast cultures from said polyploid yeast cells that stably express said antibody into the culture medium.

[1497] Clause 97A. The method of Clause 96A, wherein said yeast is of the genus *Pichia*.

[1498] Clause 98A. A method for blocking, inhibiting or neutralizing one or more biological effects associated with ACTH comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or

selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1499] Clause 99A. A method for treating or preventing a condition associated with elevated ACTH levels in a subject, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1500] Clause 100A. A method for treating or preventing a condition associated with elevated cortisol, aldosterone or corticosterone levels in a subject, comprising administering to the subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1501] Clause 101A. The method of any one of Clauses 97A-100A, wherein the condition is selected from the group consisting of ACTH-driven hypercortisolism (Cushing's Disease and/or Cushing's Syndrome), obesity, diabetes, Parkinson's disease, adrenal hyperplasia, congenital adrenal hyperplasia, sleep disorders, e.g., insomnia, sleep apnea, and narcolepsy, depression, anxiety disorders, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), muscle atrophy, hypertension, hyperinsulinemia, cognitive dysfunction, Alzheimer's disease, galactorrhea, stress related conditions, impaired cardiac function, exercise intolerance, heart failure and other cardiac conditions, metabolic syndrome, hyperaldosteronism, Conn's syndrome and familial hyperaldosteronism.

[1502] Clause 102A. A method for neutralizing ACTH-induced MCR signaling, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s)

on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1503] Clause 103A. A method for inhibiting ACTH-induced cortisol, aldosterone or corticosterone secretion, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1504] Clause 104A. A method for reducing ACTH-induced plasma cortisol, aldosterone or corticosterone levels in a subject in need thereof, comprising administering to a subject in need thereof an effective amount of a human, humanized or chimerized anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment that specifically binds to the same linear or conformational epitope(s) and/or competes for binding to the same linear or conformational epitope(s) on human ACTH as an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1505] Clause 105A. The method of any one of Clauses 98A-104A, wherein the antibody is a human, humanized or chimerized anti-ACTH antibody or antibody fragment.

[1506] Clause 106A. The method of any one of Clauses 98A-105A, wherein the antibody or antibody fragment substantially does not interact with (bind) a polypeptide consisting of: (i) the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, or (ii) the 22 C-terminal amino acid residues of ACTH ($ACTH_{18-39}$).

[1507] Clause 107A. The method of any one of Clauses 98A-106A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment inhibits the binding of ACTH to a MCR.

[1508] Clause 108A. The method of Clause 107A, wherein the MCR is selected from the group consisting of MC1R, MC2R, MC3R, MC4R and MC5R.

[1509] Clause 109A. The method of any one of Clauses 98A-108A, wherein said epitope(s) is identified using a binding assay that detects the binding of said anti-human ACTH antibody or antibody fragment to one or more peptides in a library of overlapping linear peptide fragments that span the full length of human ACTH.

[1510] Clause 110A. The method of any one of Clauses 98-109A, which contains at least 2 complementarity determining regions (CDRs) of an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1511] Clause 111A. The method of any one of Clauses 98A-110A, which contains at least 3 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1512] Clause 112A. The method of any one of Clauses 98A-110A, which contains at least 4 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1513] Clause 113A. The method of any one of Clauses 98A-110A, which contains at least 5 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1514] Clause 114A. The method of any one of Clauses 98A-110A, which contains all 6 CDRs of an anti-ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, and Ab9 or selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, and Ab12 or selected from the group consisting of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

[1515] Clause 115A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1516] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:4; a CDR2 sequence consisting of SEQ ID NO:6; and a CDR3 sequence consisting of SEQ ID NO:8;

and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:24; a CDR2 sequence consisting of SEQ ID NO:26; and a CDR3 sequence consisting of SEQ ID NO:28;

[1517] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 2; and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:22;

[1518] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:2; and/or a variable light chain having the amino acid sequence of SEQ ID NO:22; or

[1519] (d) a heavy chain having the amino acid sequence of SEQ ID NO:1, and/or a light chain having the amino acid sequence of SEQ ID NO:21.

[1520] Clause 116A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1521] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:44; a CDR2 sequence consisting of SEQ ID NO:46; and a CDR3 sequence consisting of SEQ ID NO:48, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:64; a CDR2 sequence consisting of SEQ ID NO:66; and a CDR3 sequence consisting of SEQ ID NO:68;

[1522] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:42, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:62;

[1523] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:42, and/or a variable light chain having the amino acid sequence of SEQ ID NO:62; or

[1524] (d) a heavy chain having the amino acid sequence of SEQ ID NO:41, and/or a light chain having the amino acid sequence of SEQ ID NO:61.

[1525] Clause 117A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1526] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:84; a CDR2 sequence consisting of SEQ ID NO:86; and a CDR3 sequence consisting of SEQ ID NO:88, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:104; a CDR2 sequence consisting of SEQ ID NO:106; and a CDR3 sequence consisting of SEQ ID NO:108;

[1527] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:82, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:102;

[1528] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:82, and/or a variable light chain having the amino acid sequence of SEQ ID NO:102; or

[1529] (d) a heavy chain having the amino acid sequence of SEQ ID NO:81, and/or a light chain having the amino acid sequence of SEQ ID NO:101.

[1530] Clause 118A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1531] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:124; a CDR2 sequence consisting of SEQ ID NO:126 and a CDR3 sequence consisting of SEQ ID NO:128, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:144; a CDR2 sequence consisting of SEQ ID NO:146; and a CDR3 sequence consisting of SEQ ID NO:148;

[1532] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:122 and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:142;

[1533] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:122, and/or a variable light chain having the amino acid sequence of SEQ ID NO:142; or

[1534] (d) a heavy chain having the amino acid sequence of SEQ ID NO:121, and/or a light chain having the amino acid sequence of SEQ ID NO:141.

[1535] Clause 119A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1536] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:164; a CDR2 sequence consisting of SEQ ID NO:166; and a CDR3 sequence consisting of SEQ ID NO:168, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:184; a CDR2 sequence consisting of SEQ ID NO:186; and a CDR3 sequence consisting of SEQ ID NO:188;

[1537] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:162, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:182;

[1538] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:162, and/or a variable light chain having the amino acid sequence of SEQ ID NO:182; or

[1539] (d) a heavy chain having the amino acid sequence of SEQ ID NO:161, and/or a light chain having the amino acid sequence of SEQ ID NO:181.

[1540] Clause 120A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1541] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:204; a CDR2 sequence consisting of SEQ ID NO:206; and a CDR3 sequence consisting of SEQ ID NO:208,

and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:224; a CDR2 sequence consisting of SEQ ID NO:226; and a CDR3 sequence consisting of SEQ ID NO:228;

[1542] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:202 and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:222;

[1543] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:202, and/or a variable light chain having the amino acid sequence of SEQ ID NO:222; or

[1544] (d) a heavy chain having the amino acid sequence of SEQ ID NO:201, and/or a light chain having the amino acid sequence of SEQ ID NO:221.

[1545] Clause 121A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1546] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:244; a CDR2 sequence consisting of SEQ ID NO:246; and a CDR3 sequence consisting of SEQ ID NO:248, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:264; a CDR2 sequence consisting of SEQ ID NO:266; and a CDR3 sequence consisting of SEQ ID NO:268;

[1547] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:242, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:262;

[1548] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:242, and/or a variable light chain having the amino acid sequence of SEQ ID NO:262;

[1549] (d) a heavy chain having the amino acid sequence of SEQ ID NO:241, and/or a light chain having the amino acid sequence of SEQ ID NO:261.

[1550] Clause 122A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1551] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:284; a CDR2 sequence consisting of SEQ ID NO:286; and a CDR3 sequence consisting of SEQ ID NO:288, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:304; a CDR2 sequence consisting of SEQ ID NO:306; and a CDR3 sequence consisting of SEQ ID NO:308;

[1552] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:282, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:302;

[1553] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:282, and/or a variable light chain having the amino acid sequence of SEQ ID NO:302;

[1554] (d) a heavy chain having the amino acid sequence of SEQ ID NO:281, and/or a light chain having the amino acid sequence of SEQ ID NO:301.

[1555] Clause 122.1A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1556] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:324; a CDR2 sequence consisting of SEQ ID NO:326; and a CDR3 sequence consisting of SEQ ID NO:328, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:344; a CDR2 sequence consisting of SEQ ID NO:346; and a CDR3 sequence consisting of SEQ ID NO:348;

[1557] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:322, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:342;

[1558] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:322, and/or a variable light chain having the amino acid sequence of SEQ ID NO:342;

[1559] (d) a heavy chain having the amino acid sequence of SEQ ID NO:321, and/or a light chain having the amino acid sequence of SEQ ID NO:341.

[1560] Clause 122.2A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1561] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:364; a CDR2 sequence consisting of SEQ ID NO:366; and a CDR3 sequence consisting of SEQ ID NO:368, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:384; a CDR2 sequence consisting of SEQ ID NO:386; and a CDR3 sequence consisting of SEQ ID NO:388;

[1562] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:362, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:382;

[1563] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:362, and/or a variable light chain having the amino acid sequence of SEQ ID NO:382;

[1564] (d) a heavy chain having the amino acid sequence of SEQ ID NO:361, and/or a light chain having the amino acid sequence of SEQ ID NO:381.

[1565] Clause 122.3A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1566] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:404; a CDR2 sequence consisting of SEQ ID NO:406; and a CDR3 sequence consisting of SEQ ID NO:408,

and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:424; a CDR2 sequence consisting of SEQ ID NO:426; and a CDR3 sequence consisting of SEQ ID NO:428;

[1567] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:402, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:422;

[1568] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:402, and/or a variable light chain having the amino acid sequence of SEQ ID NO:422;

[1569] (d) a heavy chain having the amino acid sequence of SEQ ID NO:401, and/or a light chain having the amino acid sequence of SEQ ID NO:421.

[1570] Clause 122.4A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1571] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:444; a CDR2 sequence consisting of SEQ ID NO:446; and a CDR3 sequence consisting of SEQ ID NO:448, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:464; a CDR2 sequence consisting of SEQ ID NO:466; and a CDR3 sequence consisting of SEQ ID NO:468;

[1572] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:442, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:462;

[1573] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:442, and/or a variable light chain having the amino acid sequence of SEQ ID NO:462;

[1574] (d) a heavy chain having the amino acid sequence of SEQ ID NO:441, and/or a light chain having the amino acid sequence of SEQ ID NO:461.

[1575] Clause 122.5A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1576] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:484; a CDR2 sequence consisting of SEQ ID NO:486; and a CDR3 sequence consisting of SEQ ID NO:488, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:504; a CDR2 sequence consisting of SEQ ID NO:506; and a CDR3 sequence consisting of SEQ ID NO:508;

[1577] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:482, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:502;

[1578] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:482, and/or a variable light chain having the amino acid sequence of SEQ ID NO:502;

[1579] (d) a heavy chain having the amino acid sequence of SEQ ID NO:481, and/or a light chain having the amino acid sequence of SEQ ID NO:501.

[1580] Clause 122.6A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1581] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:524; a CDR2 sequence consisting of SEQ ID NO:526; and a CDR3 sequence consisting of SEQ ID NO:528, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:544; a CDR2 sequence consisting of SEQ ID NO:546; and a CDR3 sequence consisting of SEQ ID NO:548;

[1582] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:522, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:542;

[1583] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:522, and/or a variable light chain having the amino acid sequence of SEQ ID NO:542;

[1584] (d) a heavy chain having the amino acid sequence of SEQ ID NO:521, and/or a light chain having the amino acid sequence of SEQ ID NO:541.

[1585] Clause 122.7A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1586] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:564; a CDR2 sequence consisting of SEQ ID NO:566; and a CDR3 sequence consisting of SEQ ID NO:568, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:584; a CDR2 sequence consisting of SEQ ID NO:586; and a CDR3 sequence consisting of SEQ ID NO:588;

[1587] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:562, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:582;

[1588] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:562, and/or a variable light chain having the amino acid sequence of SEQ ID NO:582;

[1589] (d) a heavy chain having the amino acid sequence of SEQ ID NO:561, and/or a light chain having the amino acid sequence of SEQ ID NO:581.

[1590] Clause 122.8A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1591] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:604; a CDR2 sequence consisting of SEQ ID NO:606; and a CDR3 sequence consisting of SEQ ID NO:608,

and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:624; a CDR2 sequence consisting of SEQ ID NO:626; and a CDR3 sequence consisting of SEQ ID NO:628;

[1592] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:602, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:622;

[1593] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:602, and/or a variable light chain having the amino acid sequence of SEQ ID NO:622;

[1594] (d) a heavy chain having the amino acid sequence of SEQ ID NO:601, and/or a light chain having the amino acid sequence of SEQ ID NO:621.

[1595] Clause 122.9A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1596] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:644; a CDR2 sequence consisting of SEQ ID NO:646; and a CDR3 sequence consisting of SEQ ID NO:648, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:664; a CDR2 sequence consisting of SEQ ID NO:666; and a CDR3 sequence consisting of SEQ ID NO:668;

[1597] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:642, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:662;

[1598] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:642, and/or a variable light chain having the amino acid sequence of SEQ ID NO:662;

[1599] (d) a heavy chain having the amino acid sequence of SEQ ID NO:641, and/or a light chain having the amino acid sequence of SEQ ID NO:661.

[1600] Clause 122.10A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1601] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:684; a CDR2 sequence consisting of SEQ ID NO:686; and a CDR3 sequence consisting of SEQ ID NO:688, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:704; a CDR2 sequence consisting of SEQ ID NO:706; and a CDR3 sequence consisting of SEQ ID NO:708;

[1602] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:682, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:702;

[1603] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:682, and/or a variable light chain having the amino acid sequence of SEQ ID NO:702;

[1604] (d) a heavy chain having the amino acid sequence of SEQ ID NO:681, and/or a light chain having the amino acid sequence of SEQ ID NO:701.

[1605] Clause 122.11A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1606] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:724; a CDR2 sequence consisting of SEQ ID NO:726; and a CDR3 sequence consisting of SEQ ID NO:728, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:744; a CDR2 sequence consisting of SEQ ID NO:746; and a CDR3 sequence consisting of SEQ ID NO:748;

[1607] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:722, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:742;

[1608] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:722, and/or a variable light chain having the amino acid sequence of SEQ ID NO:742;

[1609] (d) a heavy chain having the amino acid sequence of SEQ ID NO:721, and/or a light chain having the amino acid sequence of SEQ ID NO:741.

[1610] Clause 122.12A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1611] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:764; a CDR2 sequence consisting of SEQ ID NO:766; and a CDR3 sequence consisting of SEQ ID NO:768, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:784; a CDR2 sequence consisting of SEQ ID NO:786; and a CDR3 sequence consisting of SEQ ID NO:788;

[1612] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:762, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:782;

[1613] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:762, and/or a variable light chain having the amino acid sequence of SEQ ID NO:782;

[1614] (d) a heavy chain having the amino acid sequence of SEQ ID NO:761, and/or a light chain having the amino acid sequence of SEQ ID NO:781.

[1615] Clause 122.13A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1616] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:804; a CDR2 sequence consisting of SEQ ID NO:806; and a CDR3 sequence consisting of SEQ ID NO:808,

and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:824; a CDR2 sequence consisting of SEQ ID NO:826; and a CDR3 sequence consisting of SEQ ID NO:828;

[1617] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:802, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:822;

[1618] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:802, and/or a variable light chain having the amino acid sequence of SEQ ID NO:822;

[1619] (d) a heavy chain having the amino acid sequence of SEQ ID NO:801, and/or a light chain having the amino acid sequence of SEQ ID NO:821.

[1620] Clause 122.14A. The method of any one of Clauses 98A-110A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment comprises:

[1621] (a) a variable heavy chain comprising a CDR1 sequence consisting of SEQ ID NO:844; a CDR2 sequence consisting of SEQ ID NO:846; and a CDR3 sequence consisting of SEQ ID NO:848, and/or a variable light chain comprising a CDR1 sequence consisting of SEQ ID NO:864; a CDR2 sequence consisting of SEQ ID NO:866; and a CDR3 sequence consisting of SEQ ID NO:868;

[1622] (b) a variable heavy chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:842, and/or a variable light chain comprising an amino acid sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:862;

[1623] (c) a variable heavy chain having the amino acid sequence of SEQ ID NO:842, and/or a variable light chain having the amino acid sequence of SEQ ID NO:862;

[1624] (d) a heavy chain having the amino acid sequence of SEQ ID NO:841, and/or a light chain having the amino acid sequence of SEQ ID NO:861.

[1625] Clause 123A. The method of any one of Clauses 98A-122.14A, wherein the at least one anti-human ACTH antibody or antibody fragment is selected from the group consisting of chimeric, humanized, and human antibodies or antibody fragments.

[1626] Clause 124A. The method of any one of Clauses 98A-123A, wherein the at least one anti-human ACTH antibody or antibody fragment is selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR, Fab fragments, Fab' fragments, MetMab like antibodies, monovalent antibody fragments, and $F(ab')_2$ fragments.

[1627] Clause 125A. The method of any one of Clauses 98A-124A, wherein the at least one anti-human ACTH antibody or antibody fragment substantially or entirely lacks N-glycosylation and/or O-glycosylation.

[1628] Clause 126A. The method of any one of Clauses 98A-125A, wherein the at least one anti-human ACTH antibody or antibody fragment comprises a human constant domain, optionally the heavy chain constant domain polypeptide of SEQ ID NO: 886, 887, or 888.

[1629] Clause 127A. The method of any one of Clauses 98A-126A, wherein the at least one anti-human ACTH antibody or antibody fragment is an IgG1, IgG2, IgG3, or IgG4 antibody.

[1630] Clause 128A. The method of any one of Clauses 98A-127A, wherein the at least one anti-human ACTH antibody or antibody fragment comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation.

[1631] Clause 129A. The method of Clause 128A, wherein the Fc region contains one or more mutations that alters or eliminates N- and/or O-glycosylation.

[1632] Clause 130A. The method of any one of Clauses 98A-129A, wherein the at least one anti-human ACTH antibody or antibody fragment is a humanized antibody or antibody fragment.

[1633] Clause 131A. The method of any one of Clauses 98A-130A, wherein the at least one anti-human ACTH antibody or antibody fragment binds to ACTH with a K_D of less than or equal to $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M.

[1634] Clause 132A. The method of any one of Clauses 98A-131A, wherein the at least one anti-human ACTH antibody or antibody fragment binds to ACTH with a K_D of less than or equal to $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M.

[1635] Clause 133A. The method of any one of Clauses 98A-132A, wherein the at least one anti-human ACTH antibody or antibody fragment binds to ACTH with an off-rate (k_d) of less than or equal to $5x10^{-4}$ s^{-1}, 10^{-4} s^{-1}, $5x10^{-5}$ s^{-1}, or 10^{-5} s^{-1}.

[1636] Clause 134A. The method of any one of Clauses 98A-133A, wherein the at least one anti-human ACTH antibody or antibody fragment is directly or indirectly attached to a therapeutic agent.

[1637] Clause 135A. The method of any one of Clauses 98A-134A, wherein the at least one anti-human ACTH antibody or antibody fragment is attached to one or more detectable moieties.

[1638] Clause 136A. The method of Clause 135A, wherein detectable moiety comprises a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixtures thereof.

[1639] Clause 137A. The method of any one of Clauses 98A-136A, wherein the at least one anti-human ACTH antibody or antibody fragment is attached to one or more functional moieties.

[1640] Clause 138A. The method of any one of Clauses 98A-137A, wherein the at least one isolated anti-human ACTH antibody or antibody fragment reduces plasma cortisol, corticosterone and/or aldosterone levels, wherein optionally said anti-human ACTH antibody may reduce plasma

cortisol levels and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1641] Clause 139A. The method of any one of Clauses 98A-138A, wherein the method further comprises administering separately or co-administering another agent.

[1642] Clause 140A. The method of Clause 139A, wherein the other agent is selected from the group consisting of ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), and satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil (Provigil®) or wherein the other active agent is selected from the group consisting of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-I mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor

(milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), and Zestril (lisinopril).

[1643] Clause 141A. The method of Clause 139A or 140A, wherein the antibody or antibody fragment or the composition containing the antibody of antibody fragment and the at least one other agent are administered concurrently.

[1644] Clause 142A. The method of Clause 139A or 140A, wherein the antibody or antibody fragment is administered before or after the at least one other agent.

[1645] Clause 143A. The method of any one of Clauses 98A-138A, wherein the method further comprises one or more of supplemental oxygen, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), expiratory positive airway pressure (EPAP), adaptive servo-ventilation (ASV), oral applicanes, uvulopalatopharyngoplasty (UPPP), maxillomandibular advancement, nasal surgery, and removal of tonsils and/or adenoids.

[1646] Clause 1B. A human, humanized or chimerized anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment.

[1647] Clause 2B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment according to Clause 1B, which substantially does not interact with (bind) a polypeptide consisting of: (i) the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, or (ii) the 22 C-terminal amino acid residues of ACTH (ACTH) (Corticotrophin-Like Intermediate Peptide or "CLIP").

[1648] Clause 3B. The human, humanized or chimerized anti-ACTH antibody or antibody fragment according to Clause 1B, which binds to $ACTH_{1-39}$ with a binding affinity (K_D) at least 10-fold, 100-fold, 1000-fold or 10,000-fold stronger than the binding affinity of said antibody or antibody fragment to (i) $ACTH_{1-13}$ and/or alpha-MSH, and/or (ii) CLIP (i.e., a numerically lower K_D for $ACTH_{1-39}$ by at least 10-fold, 100-fold, 1000-fold or 10,000-fold relative to the K_D for $ACTH_{1-13}$ and/or alpha-MSH and/or CLIP).

[1649] Clause 4B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-3B, which is a humanized antibody or humanized antibody fragment.

[1650] Clause 5B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-3B, which is a human antibody or human antibody fragment.

[1651] Clause 6B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-5B, which is selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR, Fab fragments, Fab' fragments, MetMab like antibodies, monovalent antibody fragments, and $F(ab')_2$ fragments.

[1652] Clause 7B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-6B, which substantially or entirely lacks N-glycosylation and/or O-glycosylation.

[1653] Clause 8B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-7B, which comprises a human constant domain, optionally the heavy chain constant domain polypeptide of SEQ ID NO: 886, 887, or 888.

[1654] Clause 9B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of Clause 8B, which is an IgG1, IgG2, IgG3, or IgG4 antibody.

[1655] Clause 10B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-9B, which comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation.

[1656] Clause 11B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of Clause 10B, wherein the Fc region contains one or more mutations that alters or eliminates N- and/or O-glycosylation.

[1657] Clause 12B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-11B, which binds to ACTH with a K_D of less than or equal to $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M.

[1658] Clause 13B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-12B, which binds to ACTH with a K_D of less than or equal to $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M.

[1659] Clause 14B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-13B, which binds to ACTH with an off-rate (kd) of less than or equal to $5x10^{-4}$ s^{-1}, 10^{-4} s^{-1}, $5x10^{-5}$ s^{-1}, or 10^{-5} s^{-1}.

[1660] Clause 15B. A human, humanized or chimerized anti-ACTH antibody or antibody fragment of any one of Clauses 1B-14B, which binds to ACTH with a K_D of less than about 100 nM, less than about 10 nM, less than about 1 nM, less than about 100 pM, less than about 50 pM, less than about 40 pM, less than about 25 pM, less than about 1 pM, between about 10 pM and about 100 pM, between about 1 pM and about 100 pM, or between about 1 pM and about 10 pM.

[1661] Clause 16B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-15B, wherein the antibody or antibody fragment is directly or indirectly attached to a detectable label or therapeutic agent.

[1662] Clause 17B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-16B, which when administered to a human subject inhibits or neutralizes at least one biological effect elicited by ACTH.

[1663] Clause 18B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-17B, which neutralizes or inhibits ACTH activation of MC2R.

[1664] Clause 19B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-17B, which neutralizes or inhibits ACTH activation of at least one of MC2R, MC3R, MC4R and MC5R.

[1665] Clause 20B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-17B, which neutralizes or inhibits ACTH activation of each of MC2R, MC3R and MC4R.

[1666] Clause 21B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-17B, which inhibits ACTH-induced corticosterone secretion, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1667] Clause 22B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-17B, which when administered to a human subject reduces plasma cortisol, corticosterone and/or aldosterone levels, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1668] Clause 23B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-22B, wherein the antibody or antibody fragment is capable of inhibiting the binding of ACTH to a MCR.

[1669] Clause 24B. The anti-human ACTH antibody or antibody fragment of Clause 23B, wherein the MCR is at least one of MC1R, MC2R, MC3R, MC4R and MC5R; at least one of MC2R, MC3R, and MC4R; each of MC2R, MC3R, and MC4R; or each of MC1R, MC2R, MC3R, MC4R and MC5R.

[1670] Clause 25B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-24B, wherein the antibody or antibody fragment binds to ACTH with a K_D that is less than about 100 nM.

[1671] Clause 26B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-24B, which binds to ACTH with a K_D that is less than about 100 pM.

[1672] Clause 27B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-24B, which binds to ACTH with a K_D that is less than about 50 pM.

[1673] Clause 28B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-24B, which binds to ACTH with a K_D that is less than about 25 pM.

[1674] Clause 29B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-24B, which binds to ACTH with a K_D that is between about 10 pM and about 100 pM.

[1675] Clause 30B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-24B, which binds to ACTH with a K_D that is less than about 40 nM.

[1676] Clause 31B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-30B, which has stronger affinity for $ACTH_{1-39}$ as compared to alpha-MSH or CLIP and/or does not bind to alpha-MSH or CLIP.

[1677] Clause 32B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-31B, wherein the antibody or antibody fragment is attached to at least one effector moiety.

[1678] Clause 33B. The anti-human ACTH antibody or antibody fragment of Clause 32B, wherein effector moiety comprises a chemical linker.

[1679] Clause 34B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-33B, wherein the antibody or antibody fragment is attached to one or more detectable moieties.

[1680] Clause 35B. The anti-human ACTH antibody or antibody fragment of Clause 34B, wherein detectable moiety comprises a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixtures thereof.

[1681] Clause 36B. The anti-human ACTH antibody or antibody fragment of any one of Clauses 1B-35B, wherein the antibody or antibody fragment is attached to one or more functional moieties.

[1682] Clause 37B. An antibody produced against an anti-human ACTH antibody or anti-ACTH antibody fragment according to any one of Clauses 1B-36B.

[1683] Clause 38B. The antibody of Clause 37B, which is an anti-idiotypic antibody.

[1684] Clause 39B. A method of using an anti-idiotypic antibody or antibody fragment according to Clause 38B to detect the levels of said anti-ACTH antibody or antibody fragment and/or to neutralize said anti-ACTH antibody or antibody fragment in a subject administered said anti-ACTH antibody or antibody fragment.

[1685] Clause 40B. A composition suitable for therapeutic, prophylactic, or a diagnostic use comprising a therapeutically, prophylactically or diagnostically effective amount of at least one anti-human ACTH antibody or antibody fragment according to any one of Clauses 1B-39B.

[1686] Clause 41B. The composition of Clause 39B, which is suitable for subcutaneous administration.

[1687] Clause 42B. The composition of Clause 39B, which is suitable for intravenous administration.

[1688] Clause 43B. The composition of Clause 39B, which is lyophilized.

[1689] Clause 44B. The composition of any one of Clauses 39B-43B, further comprising a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, or mixture thereof.

[1690] Clause 45B. The composition of any one of Clauses 39B-44B, further comprising another active agent.

[1691] Clause 46B. The composition of Clause 45B, wherein the other active agent is selected from the group consisting of ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil (Provigil®) or wherein the other active agent is selected from the group consisting of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-l mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor

(milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), and Zestril (lisinopril).

[1692] Clause 47B. The composition of any one of Clauses 39B-46B, which is lyophilized, stabilized and/or formulated for administration by injection.

[1693] Clause 48B. An isolated nucleic acid sequence or nucleic acid sequences encoding an anti-human ACTH antibody or antibody fragment or anti-idiotypic antibody or antibody fragment according to any one of Clauses 1B-37B.

[1694] Clause 49B. A vector or vectors containing the isolated nucleic acid sequence or sequences of Clause 48B.

[1695] Clause 50B. A host cell comprising the isolated nucleic acid sequence or sequences of Clause 46B or the vector or vectors of Clause 49B.

[1696] Clause 51B. The host cell of Clause 50B, which is a mammalian, bacterial, fungal, yeast, avian or insect cell.

[1697] Clause 52B. The host cell of Clause 51B, which is a filamentous fungi or a yeast.

[1698] Clause 53B. The host cell of Clause 52B, wherein the yeast is selected from the from the following genera: *Arxiozyma*; *Ascobotryozyma*; *Citeromyces*; *Debaryomyces*; *Dekkera*; *Eremothecium*; *Issatchenkia*; *Kazachstania*; *Kluyveromyces*; *Kodamaea*; *Lodderomyces*; *Pachysolen*; *Pichia*; *Saccharomyces*; *Saturnispora*; *Tetrapisispora*; *Torulaspora*; *Williopsis*; and *Zygosaccharomyces*.

[1699] Clause 54B. The host cell of Clause 53B, which is the yeast genus is *Pichia*.

[1700] Clause 55B. The host cell of Clause 54B, wherein the species of *Pichia* is selected from *Pichia pastoris*, *Pichia methanolica* and *Hansenula polymorpha* (*Pichia angusta*).

[1701] Clause 56B. A method of making an anti-human ACTH antibody or antibody fragment comprising culturing the host cell of any one of Clauses 50B-55B under conditions that provide for expression of said antibody or antibody fragment.

[1702] Clause 57B. The method of Clause 56B, wherein the host cell is a polyploid yeast culture that stably expresses and secretes into the culture medium at least 10-25 mg/liter of said antibody or antibody fragment.

[1703] Clause 58B. The method of Clause 57B, wherein said polyploidal yeast is made by a method that comprises:

[1704] (i) introducing at least one expression vector containing one or more heterologous polynucleotides encoding said antibody operably linked to a promoter and a signal sequence into a haploid yeast cell;

[1705] (ii) producing by mating or spheroplast fusion a polyploidal yeast from said first and/or second haploid yeast cell;

[1706] (iii) selecting polyploidal yeast cells that stably express said antibody; and

[1707] (iv) producing stable polyploidal yeast cultures from said polyploidal yeast cells that stably express said antibody into the culture medium.

[1708] Clause 59B. The method of Clause 58B, wherein said yeast is of the genus *Pichia*.

[1709] Clause 60B. A method for blocking, inhibiting or neutralizing one or more biological effects associated with ACTH comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment.

[1710] Clause 61B. A method for treating or preventing a condition associated with elevated ACTH levels in a subject, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment.

[1711] Clause 62B. A method for treating or preventing a condition associated with elevated cortisol, corticosterone and/or aldosterone levels in a subject, comprising administering to the subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels, and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1712] Clause 63B. The method of any one of Clauses 60B-62B, wherein the condition is selected from the group consisting of ACTH-driven hypercortisolism (Cushing's Disease and/or Cushing's Syndrome), obesity, diabetes, Parkinson's disease, sleep disorders including e.g., insomnia, sleep apnea, adrenal hyperplasia, congenital adrenal hyperplasia, narcolepsy, depression, anxiety disorders, cancer (such as Cushing's Syndrome resulting from ectopic ACTH expression, e.g., in small cell lung cancer, non-small cell lung cancer (NSCLC), pancreatic carcinoma, neural tumors, or thymoma), muscle atrophies, hypertension, Alzheimer's disease, dementia and other cognitive dysfunction disorders, Alzheimer's disease, galactorrhea, stress related disorders, heart failure, diabetes, hyperinsulinemia, metabolic syndromes, hyperaldosteronism, Conn's syndrome and familial hyperaldosteronism.

[1713] Clause 64B. A method for neutralizing ACTH-induced MCR signaling, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment.

[1714] Clause 65B. A method for inhibiting ACTH-induced cortisol, corticosterone and/or aldosterone secretion, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels, and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1715] Clause 66B. A method for reducing ACTH-induced plasma cortisol, corticosterone and/or aldosterone levels in a subject in need thereof, comprising administering to the subject in need thereof an effective amount of a human, humanized or chimerized anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels, and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1716] Clause 67B. The method of any one of Clauses 60B-66B, wherein the antibody is a human, humanized or chimerized anti-ACTH antibody or antibody fragment

[1717] Clause 68B. The method of any one of Clauses 60B-67B, wherein the antibody or antibody fragment substantially does not interact with (bind) a polypeptide consisting of: (i) the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, or (ii) the 22 C-terminal amino acid residues of ACTH ($ACTH_{18-39}$).

[1718] Clause 69B. The method of any one of Clauses 60B-68B, wherein the at least one anti-human ACTH antibody or antibody fragment is selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR, Fab fragments, Fab' fragments, MetMab like antibodies, monovalent antibody fragments, and $F(ab')_2$ fragments.

[1719] Clause 70B. The method of any one of Clauses 60B-69B, wherein the at least one anti-human ACTH antibody or antibody fragment substantially or entirely lacks N-glycosylation and/or O-glycosylation.

[1720] Clause 71B. The method of any one of Clauses 60B-70B, wherein the at least one anti-human ACTH antibody or antibody fragment comprises a human constant domain, optionally the heavy chain constant domain polypeptide of SEQ ID NO: 886, 887, or 888.

[1721] Clause 72B. The method of any one of Clauses 60B-71B, wherein the at least one anti-human ACTH antibody or antibody fragment is an IgG1, IgG2, IgG3, or IgG4 antibody.

[1722] Clause 73B. The method of any one of Clauses 60B-72B, wherein the at least one anti-human ACTH antibody or antibody fragment comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation.

[1723] Clause 74B. The method of Clause 73B, wherein the Fc region contains one or more mutations that alters or eliminates N- and/or O-glycosylation.

[1724] Clause 75B. The method of any one of Clauses 60B-74B, wherein the at least one anti-human ACTH antibody or antibody fragment is a humanized antibody or antibody fragment.

[1725] Clause 76B. The method of any one of Clauses 60B-75B, wherein the at least one anti-human ACTH antibody or antibody fragment binds to ACTH with a K_D of less than or equal to $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M.

[1726] Clause 77B. The method of any one of Clauses 60B-76B, wherein the at least one anti-human ACTH antibody or antibody fragment binds to ACTH with a K_D of less than or equal to 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, or 10^{-12} M.

[1727] Clause 78B. The method of any one of Clauses 60B-77B, wherein the at least one anti-human ACTH antibody or antibody fragment binds to ACTH with an off-rate (kd) of less than or equal to $5x10^{-4}$ s^{-1}, 10^{-4} s^{-1}, $5x10^{-5}$ s^{-1}, or 10^{-5} s^{-1}.

[1728] Clause 79B. The method of any one of Clauses 60B-78B, wherein the at least one anti-human ACTH antibody or antibody fragment is directly or indirectly attached to a therapeutic agent.

[1729] Clause 80B. The method of any one of Clauses 60B-79B, wherein the at least one anti-human ACTH antibody or antibody fragment is attached to one or more detectable moieties.

[1730] Clause 81B. The method of Clause 80B, wherein detectable moiety comprises a fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, or mixtures thereof.

[1731] Clause 82B. The method of any one of Clauses 60B-81B, wherein the at least one anti-human ACTH antibody or antibody fragment is attached to one or more functional moieties.

[1732] Clause 83B. The method of any one of Clauses 60B-82B, wherein the at least one isolated anti-human ACTH antibody or antibody fragment reduces plasma cortisol, corticosterone and/or aldosterone levels, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels, and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1733] Clause 84B. The method of any one of Clauses 60B-83B, wherein the method further comprises administering separately or co-administering another agent.

[1734] Clause 85B. The method of Clause 84B, or wherein the other agent is selected from the group consisting of ketoconazole (Nizoral®), aminoglutethimide (Cytadren®), metyrapone (Metopirone®), mitotane (Lysodren®) etomidate (Amidate®), cyproheptadine (Periactin® or Peritol®), valproic acid (Depakote®), cabergoline (Dostinex®), pasireotide (Signifor®), rosiglitazone (Avandia®), conivaptan (Vaprisol®), tolvaptan (OPC-41061), lixivaptan (VPA-985), satavaptan (SR121463, planned trade name Aquilda®), mifepristone (Korlym®), armodafinil (Nuvigil®) and modafinil (Provigil®) or wherein the other active agent is selected from the group consisting of: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone

receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-I mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin (benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor (milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), and Zestril (lisinopril).

[1735] Clause 86B. The method of Clause 84B or 85B, wherein the antibody or antibody fragment or the composition containing the antibody of antibody fragment and the at least one other agent are administered concurrently.

[1736] Clause 87B. The method of Clause 84B or 85B, wherein the antibody or antibody fragment is administered before or after the at least one other agent.

[1737] Clause 88B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-ACTH antibody or antibody fragment which substantially does not interact with (bind) a polypeptide consisting of: (i) the 13 N-terminal amino acid residues of ACTH ($ACTH_{1-13}$) and/or alpha-MSH, or (ii) the 22 C-terminal amino acid residues of ACTH ($ACTH_{18-39}$) (Corticotrophin-Like Intermediate peptide or "CLIP").

[1738] Clause 89B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-ACTH antibody or antibody fragment which binds to $ACTH_{1-39}$ with a binding affinity (K_D) at least 10-fold, 100-fold, 1000-fold or 10,000-fold stronger than the binding affinity of said antibody or antibody fragment to (i) $ACTH_{1-13}$ and/or alpha-MSH, and/or (ii) CLIP (i.e., a numerically lower K_D for $ACTH_{1-39}$ than for $ACTH_{1-13}$ and/or alpha-MSH and/or CLIP by at least 10-fold, 100-fold, 1000-fold or 10,000-fold).

[1739] Clause 90B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment which neutralizes or inhibits ACTH activation of MC2R.

[1740] Clause 91B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment which neutralizes or inhibits ACTH activation of at least one of MC2R, MC3R and MC4R.

[1741] Clause 92B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment, which neutralizes or inhibits ACTH activation of each of MC2R, MC3R and MC4R.

[1742] Clause 93B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment, which inhibits ACTH-induced corticosterone secretion, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels, and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1743] Clause 94B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment, which when administered to a human subject reduces plasma cortisol, corticosterone and/or aldosterone levels, wherein optionally said anti-human ACTH antibody may reduce plasma cortisol levels, and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels.

[1744] Clause 95B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment capable of inhibiting the binding of ACTH to a MCR.

[1745] Clause 96B. The method of any one of Clauses 60B-87B, wherein the anti-ACTH antibody or antibody fragment is a human, humanized or chimerized anti-human ACTH antibody or antibody fragment, capable of inhibiting the binding of ACTH to at least one of MC1R, MC2R, MC3R, MC4R and MC5R; at least one of MC2R, MC3R, and MC4R; each of MC2R, MC3R, and MC4R; or each of MC1R, MC2R, MC3R, MC4R and MC5R.

[1746] Clause 97B. The method of any one of Clauses 60B-83B, wherein the method further comprises one or more of supplemental oxygen, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), expiratory positive airway pressure (EPAP), adaptive servo-ventilation (ASV), oral applicanes, uvulopalatopharyngoplasty (UPPP), maxillomandibular advancement, nasal surgery, and removal of tonsils and/or adenoids.

[1747] The entire disclosure of each document cited herein (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) including all references cited herein (including, without limitation thereto, in the Background, Detailed Description, and Examples) is hereby incorporated by reference in its entirety.

[1748] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (*e.g.* amounts, temperature, concentrations, *etc.*) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

EXAMPLES

[1749] ***Example 1 Preparation of Antibodies that Selectively Bind ACTH***

[1750] By using an antibody selection protocol substantially as described herein, a panel of antibodies specific to ACTH was produced.

[1751] Immunization Strategy

[1752] Rabbits were immunized with ACTH 1-24 (Bachem, Torrance, CA) (SEQ ID NO:882) or ACTH 1-39 (Bachem) (SEQ ID NO:881). Peptides were prepared for immunization as follows. A volume of 1ml of 10mg/ml KLH was dissolved in DPBS supplemented to 1M NaCl and combined with 0.5ml of 5mg/ml peptide (dissolved in deionized water). Then 1.4ml of 40mM Carbodiimide was added prior to a 12-hour incubation at room temperature with gentle mixing. Excess Carbodiimide

and unconjugated peptide were removed by dialysis to DPBS prior to sterile filtration. Next unconjugated peptide equal to the calculated mass of KLH was added to make a final total protein concentration of 3.75mg/ml.

[1753] Immunizations were performed by diluting 200 µg of antigen to 0.5ml with DPBS and mixing with an equal volume of complete Freund's adjuvant for subcutaneous 1ml injection at Day 1.

[1754] Boost injections of 100ug were performed at Day 21, 42 and 60.

[1755] Antibody Selection Titer Assessment

[1756] To identify antibodies that neutralize ACTH 1-39 (SEQ ID NO:881) induced signaling via MC2R, polyclonal antibody solutions were first purified via Protein A and dialyzed into a neutral buffer. Briefly, antibody solutions were incubated with ACTH 1-39 (SEQ ID NO:881) at 3x the final concentration (100pM) for 1hr. While the antibody/antigen complexes were incubated, MC2R expressing cells (Life Technologies, Grand Island, NY) were detached with 0.25% trypsin for 4 minutes. The cells were washed and re-suspended at $2x10^6$ cells per ml in assay buffer (Meso Scale Discovery [MSD], Rockville, MD) and treated with 0.2mM IBMX (Sigma, St. Louis MO). Ten microliters of cells was combined with 20µl of Ab/Ag mixture and added to a cAMP plate (MSD) and incubated for 30 minutes at room temperature with shaking. Next 20µl of labeled cAMP in cell lysis buffer (MSD) was added and incubated for 1 hour while shaking. Following the incubation, 100µl read buffer (MSD) was added and read with a Sector Imager 2400.

[1757] Tissue Harvesting

[1758] Once acceptable titers were established, the rabbit(s) were sacrificed. Spleen, lymph nodes, and whole blood were harvested and processed as follows:

[1759] Spleen and lymph nodes were processed into a single cell suspension by disassociating the tissue and pushing through sterile wire mesh at 70 µm (Fisher) with a plunger of a 20 cc syringe. Cells were collected in PBS. Cells were washed twice by centrifugation. After the last wash, cell density was determined by trypan blue. Cells were centrifuged at 1500 RPM for 10 minutes; the supernatant was discarded. Cells were resuspended in the appropriate volume of 10% dimethyl sulfoxide (DMSO, Sigma) in FBS (Hyclone) and dispensed at 1ml/vial. Vials were stored at -70°C in a slow freezing chamber for 24 hours and stored in liquid nitrogen.

[1760] Peripheral blood mononuclear cells (PBMCs) were isolated by mixing whole blood with equal parts of PBS. 35ml of the whole blood mixture was carefully layered onto 8ml of Lympholyte® Rabbit (Cedarlane, Burlington, Ontario, Canada) into a 45ml conical tube (Corning) and centrifuged 30 minutes at 2500 RPM at room temperature without brakes. After centrifugation, the PBMC layers were carefully removed using a glass Pasteur pipette (VWR), combined, and placed into a clean 50 mL vial. Cells were washed twice with PBS by centrifugation at 1500 RPM for 10 minutes at room temperature, and cell density was determined by trypan blue staining. After the last wash, cells were resuspended in an appropriate volume of 10% DMSO/FBS medium and frozen as described above.

[1761] B cell selection, enrichment and culture conditions

[1762] On the day of setting up B cell culture, PBMC, splenocyte, or lymph node vials were thawed for use. Vials were removed from LN2 tank and placed in a 37°C water bath until thawed. Contents of vials were transferred into 15 mL conical centrifuge tube (Corning) and 10 mL of modified RPMI was slowly added to the tube. Cells were centrifuged for 5 minutes at 2K RPM, and the supernatant was discarded. Cells were resuspended in 10 mL of fresh media. Cell density and viability was determined by trypan blue.

[1763] For positive selection of anti-ACTH producing B-cells, biotinylated human ACTH 1-39 (SEQ ID NO:881) was pre-loaded onto the streptavidin beads as follows. Seventy-five microliters of streptavidin beads (Miltenyi Biotec, Auburn CA) were mixed with N-terminally biotinylated human ACTH 1-39 (1μg/mL final concentration) and 300 μl of PBS supplemented with 0.5% biotin free BSA and 2mM EDTA (PBF). This mixture was incubated at 4°C for 30 minutes and unbound biotinylated human ACTH 1-39 (Bachem) was removed using a MACS® separation column (Miltenyi Biotec) with a 1ml rinse to remove unbound material. Then bound material was plunged out by detachment from the magnet and used to resuspend cells from above in 100 μL per $1X10^7$ cells. The mixture was then incubated at 4 °C for 30 minutes and washed once with 10 mL of PBF. After washing, the cells were resuspended in 500 μL of PBF and set aside. A MACS® MS column (Miltenyi Biotec) was pre-rinsed with 500 μL of PBF on a magnetic stand (Miltenyi Biotec). Cell suspension was applied to the column through a pre-filter, and unbound fraction was collected. The column was washed with 2.5 mL of PBF buffer. The column was removed from the magnet stand and placed onto a clean, sterile 1.5 mL Eppendorf tube. 1 mL of PBF buffer was added to the top of the column, and positive selected cells were collected. The yield and viability of positive cell fraction was determined by trypan blue staining. Positive selection yielded an average of 1% of the starting cell concentration.

[1764] A pilot cell screen was established to provide information on seeding levels for the culture. Plates were seeded at 5, 10, 25, 50, 100, or 200 enriched B cells/well. In addition, each well contained 25-50K cells/well of irradiated EL-4.B5 cells (5,000 Rads) and an appropriate level of activated rabbit T cell supernatant (*See* U.S. Patent Application Publication No. 20070269868) (ranging from 1-5% depending on preparation) in high glucose modified RPMI medium at a final volume of 250 μL/well. Cultures were incubated for 5 to 7 days at 37 °C in 4% CO_2.

[1765] B-Cell culture screening by antigen-recognition (ELISA)

[1766] To identify wells producing anti-human ACTH antibodies, B-cell supernatants were tested by antigen-recognition (ELISA). Briefly, neutravidin coated plates (Thermo Scientific), were coated with N-term biotinylated human ACTH 1-39 (Bachem) (50μl per well; 1μg/ml) diluted in ELISA buffer (0.5% fish skin gelatin in PBS pH 7.4) either for approximately 1 hour at room temperature or alternatively overnight at 4°C. The plates were then further blocked with ELISA buffer for one hour at

room temperature and washed using wash buffer (PBS, 0.05% Tween 20). B-cell supernatant samples (50µL) were transferred onto the wells and incubated for one hour at room temperature. After this incubation, the plate was washed with wash buffer. For development, an anti-rabbit specific Fc-HRP (1:5000 dilution in ELISA buffer) was added onto the wells and incubated for 45 minutes at room temperature. After a 3X wash step with wash solution, the plate was developed using TMB substrate for two minutes at room temperature and the reaction was quenched using 0.5M HCl. The well absorbance was read at 450nm.

[1767] To identify wells producing anti-human ACTH antibodies that do not recognize ACTH 1-13 (SEQ ID NO:883) or ACTH 18-39 (SEQ ID NO:884), supernatant from wells positive for ACTH 1-39 binding by ELISA were tested by ELISA for binding to ACTH 1-13 and ACTH 18-39. Briefly, a mixture of biotinylated ACTH 1-13 (SEQ ID NO:881) and ACTH 18-39 (SEQ ID NO:884) was bound onto Neutravidin coated plates (50µg per well, 1µg/µl each peptide). B-cell supernatant samples (50µl) were tested without prior dilution. Recognition in this assay indicates cross reactivity with sub-peptide products of ACTH.

[1768] Identification of functional activity in B-cell supernatants using one or more assays

[1769] To identify wells producing anti-human ACTH antibodies that block signaling of ACTH via MC2R, supernatant from positive wells for ACTH 1-39 binding by ELISA were tested in the cAMP assay (MSD) with MC2R expressing cells (Life Technologies). Supernatants (76µl) were pre-incubated with 4µl of a solution containing 3nM ACTH 1-39 (Bachem) for 1 hour at room temperature. During the incubation, MC2R cells were prepared as described for titer assessment. Cells (10µl) and antigen/antibody complex (20µl) were incubated together in a cAMP assay plate (MSD) and incubated at room temperature for 30 minutes while shaking. Following the incubation, 20µl of labeled cAMP in lysis buffer (MSD) was added and the plate was incubated for 1 hour while shaking. After the final incubation, 100µl of 1.5x read buffer (MSD) was added and plates read with a SECTOR® Imager 2400.

[1770] Alternatively, the supernatants were tested in a similar assay to determine the ability to block signaling of ACTH in MC2R expressing cells via cAMP accumulation with a cAMP HTRF assay (Cisbio). Supernatants (78µl) were pre-incubated 2µl 5nM ACTH 1-39 (Bachem) for 1 hour at 37C. During the incubation, MC2R cells were prepared as described for titer assessment. Cells (10µl) and antigen/antibody complex (40µl) were transferred to an HTRF plate and shaken at room temperature for 30 minutes. Following the incubation, 20µl of (1:20 diluted) Eu3+ cryptate-labeled MAb anti-cAMP and 20µl of (1:20 diluted) d2-labeled cAMP was added and the plate was incubated for 1 hour while shaking. Following incubation plates were read (excitation 330, emission 620/665nM) and a ratio of 620:665 signal was determined.

[1771] Isolation of antigen-specific B cells

[1772] Antigen-specific B cells were isolated (for general methods see co-owned publication no. WO/2014/146074, which is hereby incorporated by reference in its entirety). Plates containing wells of interest were removed from –70 °C, and the cells from each well were recovered using five washes of 200 microliters of medium (10% RPMI complete, 55μM BME) per well. The recovered cells were pelleted by centrifugation and the supernatant was carefully removed. Cells from each well were then re-suspended in 100μl of medium and transferred to a 96 well plate. Cells were incubated for 90 minutes at 37°C. Following incubation, cells were pelleted by centrifugation, stained with a FITC-labeled anti-rabbit IgG (final concentration 6.25μg/ml) (Creative Diagnostics, Shirley, NY) and washed with up to 2 milliliters FACS buffer (Dulbecco's PBS w/ 2%FBS) and re-suspended in 250ul of FACS buffer.

[1773] Control wells from the same culture sets that were similar in composition to pooled wells of interest were thawed and stained along side target wells. These samples were initially run on FACS (BD Influx) and gates were established for IgG, viability and physical parameters (FSC/SSC) that differentiate B cells from the murine EL4 cells. Once gates were established, the sample of interest was run and IgG positive, viable cells that are of a consistent physical (FSC/SSC) population were sorted individually into wells of a 96 well plate pre-loaded with RT-PCR master mix. Upwards of 8 cells per well were sorted. Sorted plates were removed from the sorter and transferred directly to thermocyclers for PCR.

[1774] Amplification and sequence determination of Antibody Sequences From FACS-sorted B Cells

[1775] Antibody sequences were recovered using a combined RT-PCR based method from a single cell sorted B-cell. Primers containing restriction enzymes were designed to anneal in conserved and constant regions of the target immunoglobulin genes (heavy and light), such as rabbit immunoglobulin sequences, and a two-step nested PCR recovery was used to amplify the antibody sequence. Amplicons from each well were sequenced and analyzed. Representative antibodies from the resulting sequence clusters are selected for recombinant protein expression. The original heavy and light variable regions amplified from rabbit cells are cloned into human heavy and light chain constant region expression vectors via restriction enzyme digestion and ligation. Vectors containing subcloned DNA fragments were amplified and purified. The sequences of the subcloned heavy and light chains were verified prior to expression.

[1776] Recombinant Production of Monoclonal Antibody of Desired Antigen Specificity and/or Functional Properties

[1777] To determine antigen specificity and functional properties of recovered antibodies from specific B-cells, the heavy and light chain plasmids were co-transfected to generate rabbit/human chimeric antibodies for testing. Briefly, heavy and light chimeric plasmids were transiently transfected into HEK-293 cells. Transfections were allowed to incubate for 5-7 days and upon

harvest cells were pelleted by centrifugation. Supernatants were submitted for purification via Protein A. Resulting purified chimeric antibodies were then evaluated in a variety of assays to confirm specificity and potency.

[1778] Antigen-recognition of recombinant antibodies by ELISA

[1779] To characterize recombinant expressed antibodies for their ability to bind to human ACTH 1-39 antibody-containing solutions were tested by ELISA. All incubations were done at room temperature. Briefly, N-term biotinylated human ACTH 1-39 was bound onto Neutravidin coated plates (Thermo Scientific) (50µl per well, 1µg/mL) in PBS) for 2 hours. ACTH-coated plates were then washed three times in wash buffer (PBS, 0.05% Tween-20). The plates were then blocked using a blocking solution (PBS, 0.5% fish skin gelatin, 0.05% Tween-20) for approximately one hour. The blocking solution was then removed and the plates were then incubated with a dilution series of the antibody being tested for approximately one hour. At the end of this incubation, the plate was washed three times with wash buffer and further incubated with a secondary antibody containing solution (Peroxidase conjugated AffiniPure™ $F(ab')_2$ fragment goat anti-human IgG, Fc fragment specific (Jackson Immunoresearch) for approximately 45 minutes and washed three times. Next a substrate solution (TMB peroxidase substrate, BioFx®, SurModics, Eden Prairie, MN) was added and incubated for 3 to 5 minutes in the dark. The reaction was stopped by addition of 0.5M HCl and the plate was read at 450 nm in a plate-reader.

[1780] Alternatively, To characterize recombinant expressed antibodies for their ability to preferentially bind ACTH 1-39 and not ACTH 1-13 or ACTH 18-39 (respectively containing the amino acids contained in alpha-MSH and CLIP), a competition HTRF ELISA was performed. In parallel, 10µl of an antibody dilution series (highest final concentration of 100nM) were incubated with 10µl of N-term biotinylated human ACTH 1-39 (67nM final) alone or in combination with either (i) ACTH 1-13 (55nM final) and ACTH 18-39 (55nM final), or (ii) ACTH 1-13 (550nM final) and ACTH 18-39 (550nM final) in a HTRF plate. Twenty microliters of Eu3+ cryptate labeled anti-hu Fc donor and 20µl of d2-labeled streptavidin acceptor were added to each well and incubated for 1 hour at room temperature. Fluorescence was measured at 620 and 665nM with a delay of 300 µsec.

[1781] Results

[1782] Using the above-described methods, numerous functional (antagonistic) antibodies that bind intact human ACTH, but which do not, or do not appreciably bind to alpha-MSH or CLIP were identified. Polypeptide and exemplary coding sequences of these antibodies (including humanized variants thereof) are contained in the included biological sequence listing and illustrated in FIGs. 1-12. The binding and functional properties of exemplary anti-ACTH antibodies produced according to the invention are further described below.

[1783] FIG. 13 is representative of binding curves for the subject anti-ACTH antibodies for human ACTH (showing results for Ab1). EC50 values were computed for each antibody based upon

their binding curves and are shown in Table 1 below. The results demonstrate that Ab1-Ab7 and Ab9-Ab12 bind to and recognize human ACTH with high affinity, ranging between EC50 values of 0.24 nM and 2.24 nM.

[1784] Table 1. Binding (EC50) of Ab1-Ab7 and Ab9-Ab12 for human ACTH.

ANTIBODY	huACTH 1-39 EC_{50} nM
Ab1	0.48
Ab2	0.42
Ab3	0.24
Ab4	0.39
Ab5	1.50
Ab6	2.00
Ab7	2.24
Ab9	2.05
Ab10	1.57
Ab11	0.81
Ab12	0.76

[1785] Additionally, anti-human ACTH antibodies that do not recognize ACTH 1-13 (SEQ ID NO:882) or ACTH 18-39 (SEQ ID NO:884) were identified by ELISA. Briefly, neutravidin plates (Thermo Scientific) were coated with a mixture of biotinylated ACTH 1-13 and ACTH 18-39 (50µl per well, 1µg/ml each peptide) and the ELISA assay run as described above.

[1786] Results: FIG. 14 shows representative binding curves for an anti-ACTH antibody (specifically, Ab1) for ACTH 1-13 or ACTH 18-39. Based upon these results, the EC50 was determined to be > 10 µM in all instances, as shown in Table 2, indicating at most relatively low specific binding (or no specific binding).

[1787] Table 2. Binding (EC50) of Ab1-Ab7 and Ab9-Ab12 for human ACTH 1-13 and human ACTH 18-39.

ANTIBODY	huACTH 1-13 EC_{50}	huACTH 18-39 EC_{50}
Ab1	>10 µM	>10 µM
Ab2	>10 µM	>10 µM
Ab3	>10 µM	>10 µM
Ab4	>10 µM	>10 µM
Ab5	>10 µM	>10 µM
Ab6	>10 µM	>10 µM
Ab7	>10 µM	>10 µM
Ab9	>10 µM	>10 µM
Ab10	>10 µM	>10 µM
Ab11	>10 µM	>10 µM

Ab12	>10 μM	>10 μM

[1788] Alternatively, to identify antibodies that preferentially bind ACTH 1-39 (SEQ ID NO:881) and not ACTH 1-13 (SEQ ID NO:883) or ACTH 18-39 (SEQ ID NO:884) sub-peptides of full length ACTH (i.e., corresponding to the amino acids contained in alpha-MSH and CLIP, respectively), a competition HTRF ELISA was performed.

[1789] In parallel, 10μl of an antibody dilution series (highest final concentration of 100nM) were incubated with 10μl of N-term biotinylated human ACTH 1-39 (67nM final) alone or in combination with either (i) ACTH 1-13 (55nM final) and ACTH 18-39 (55nM final), or (ii) ACTH 1-13 (550nM final) and ACTH 18-39 (550nM final) in a HTRF plate. Twenty microliters of Eu3+ cryptate labeled anti-hu Fc donor and 20μl of d2-labeled streptavidin acceptor were added to each well and incubated for 1 hour at room temperature. Fluorescence was measured at 620 and 665nM with a delay of 300 μsec.

[1790] Results

[1791] FIG. 15 provides representative binding data for the subject anti-human ACTH antibodies to ACTH 1-39 and the inability of human ACTH 1-13 and ACTH 18-39 to compete with binding of ACTH 1-39 (specifically, for Ab5). Similar lack of effects of human ACTH 1-13 and ACTH 18-39 on binding to ACTH 1-39 were observed for Ab6-Ab7 and Ab9-Ab12 (not shown). The lack of effect of ACTH 1-13 and ACTH 18-39 on binding to ACTH 1-39 is also reflected in the EC50 values of > 10 μM for these fragments indicated in Table 2 above. These results demonstrate that Ab5-Ab7 and Ab9-Ab12 bind to ACTH 1-39 but do not bind (or do not appreciably bind) ACTH 1-13 or ACTH 18-39.

[1792] Humanized forms of antibodies Ab1, Ab2, Ab3, Ab4, Ab6, Ab7, Ab10, Ab11, and Ab12 were produced and are identified by an appended ".H", i.e., Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab10.H, Ab11.H, and Ab12.H. Further variants of the humanized Ab7.H and Ab11.H sequences were also produced and are identified as Ab7A.H and Ab11A.H, respectively.

[1793] Functional characterization of antibodies by cAMP assay

[1794] The ability of anti-ACTH antibodies to neutralize ACTH-induced MC2R signaling was tested in a cell-based assay.

[1795] For Ab1-Ab4, to identify antibodies that neutralize ACTH-induced signaling via MC2R, antibody solutions were incubated with ACTH 1-39 at 3x the final concentration (100pM) for 1hour. While the antibody/antigen complexes were incubated, MC2R cells were detached with 0.25% trypsin for 4 minutes. The cells were washed and re-suspended at $2x10^6$ cells per ml in assay buffer (MSD) and treated with 0.2mM IBMX. Ten microliters of cells was combined with 20μl of antigen/antibody mixture and added to a cAMP plate (MSD) and incubated for 30 minutes at room temperature while shaking. After the incubation, 20μl of labeled cAMP in cell lysis buffer (MSD) was added and

incubated 1 hour while shaking. Following last incubation 100µl of 1.5X MSD read buffer was added and read with Sector Imager 2400.

[1796] Results: FIG. 16 shows an inhibition curve (for Ab1) that is representative of the inhibition curves obtained with the other tested antibodies. The inhibition results were quantified for each antibody to yield an IC50 value, which are summarized in Table 3 below. These results demonstrated that anti- ACTH 1-39 antibodies Ab1-Ab4 inhibited ACTH induced cAMP in cells expressing MC2R.

[1797] Table 3. Inhibition (IC50) of ACTH induced cAMP in cells expressing MC2R by anti-ACTH antibodies.

ANTIBODY	MC2R IC_{50} nM
Ab1	0.14
Ab2	0.25
Ab3	0.29
Ab4	0.46
Ab5	0.11
Ab6	0.03
Ab7	0.09
Ab9	0.12
Ab10	0.16
Ab11	0.03
Ab12	0.05
Ab1.H	0.01
Ab2.H	0.05
Ab3.H	0.15
Ab4.H	0.03
Ab6.H	0.06
Ab7.H	0.11
Ab7A.H	0.09
Ab10.H	0.01
Ab11.H	0.02
Ab11A.H	0.08
Ab12.H	0.05

[1798] Alternatively, for Ab5-Ab7, Ab9-Ab12, Ab1.H-Ab7.H, Ab7A.H, Ab10.H-Ab12.H, and Ab11A.H, to identify antibodies that neutralize ACTH 1-39 induced signaling via MC2R, antibody solutions were incubated with ACTH (1-39) at 4x the final concentration (100pM) for 1hr. While the antibody/antigen complexes were incubated for 1 hour, MC2R cells (Life Technologies) were detached with 0.25% trypsin for 4 minutes. The cells were washed and re-suspended at $1x10^6$ cells per ml culture media. Twenty microliters of Ab/antigen mixture was mixed with 20µl of cells in HTRF plates and incubated with shaking for 30 minutes. Twenty microliters of Eu3+ cryptate labeled

anti-cAMP MAb and 20µl d2-labeled cAMP was added to each well and incubated for 1 hour with shaking. Fluorescence was measured at 620 and 665nM with a delay of 300 µsec.

[1799] Results

[1800] FIG. 17 is representative of the inhibition curves obtained by this method (results are shown for Ab5). The computed IC50 values for each antibody (shown in Table 3 above) demonstrate that Ab5-Ab7, Ab9-Ab12, Ab1.H-Ab7.H, Ab7A.H, Ab10.H-Ab12.H, and Ab11A.H inhibited ACTH-induced cAMP in cells expressing MC2R.

[1801] ***Example 2***

[1802] Binding Affinities of anti-ACTH Antibodies

[1803] Binding affinities of monoclonal antibodies for human and mouse ACTH were estimated using Surface Plasmon Resonance (SPR) on the ProteOn™ XPR36 (Bio-Rad, Hercules, CA). Antibody was immobilized to the surface of general amine coupling (GLC or GLM) Chips (Bio-Rad). A dilution series of human ACTH 1-39 (SEQ ID NO:881) prepared in 1x HBS-EP+ Buffer (10mM Hepes; 150mM NaCl; 3mM EDTA, 0.05% Polysorbate 20; pH 7.6 at 25°C) purchased from Thermo Scientific and supplemented with 0.2 mg/mL Bovine Serum Albumin (BSA) from Jackson ImmunoResearch and 0.005% sodium azide from VWR was used to query the antibodies. At the chosen concentrations of antigen (ranging from 454 ng/ml to 5.6 ng/ml) association times of 200 seconds and dissociation times of 30-200 minutes were used with the ProteOn™ Manager Software (v3.1.0.6, Bio-Rad) to group and fit data using a 1:1 Langmuir binding model. Surfaces were regenerated between analyte queries using 10 mM glycine at pH 2.0. Data repeated across a single density was averaged and a single K_D and standard propagation of error calculated for each antibody.

[1804] The same procedure was used to determine binding affinities of antibodies for human alpha-MSH (ACTH 1-13) (SEQ ID NO:883) and CLIP (ACTH 18-39) (SEQ ID NO:884) except peptide concentrations ranged from 1.66 µg/ml to 0.02 µg/ml and 2.46 µg/ml to 0.03 µg/ml respectively with an association time of 200 seconds and dissociation times of 1-10 minutes.

[1805] The measured antibody affinities for ACTH are listed in Table 4.

[1806] TABLE 4.

Antibody	Ka (1/Ms)	Kd (1/s)	K_D (M)
Ab1	1.0×10^{6}	1.9×10^{-4}	1.9×10^{-10}
Ab2	1.0×10^{6}	1.3×10^{-4}	1.3×10^{-10}
Ab3	8.2×10^{5}	1.5×10^{-5}	1.8×10^{-11}
Ab4	1.0×10^{6}	2.7×10^{-4}	2.7×10^{-10}
Ab5	1.0×10^{6}	6.4×10^{-5}	6.4×10^{-11}

Ab6	1.0×10^{6}	1.9×10^{-5}	1.9×10^{-11}
Ab7	1.0×10^{6}	3.7×10^{-5}	3.7×10^{-11}
Ab9	9.1×10^{5}	4.7×10^{-5}	5.2×10^{-11}
Ab10	1.0×10^{6}	1.1×10^{-4}	1.1×10^{-10}
Ab11	1.0×10^{6}	4.0×10^{-5}	4.0×10^{-11}
Ab12	8.2×10^{5}	9.8×10^{-5}	1.2×10^{-10}
Ab1.H	8.0×10^{5}	5.1×10^{-5}	6.3×10^{-11}
Ab2.H	8.9×10^{5}	1.6×10^{-4}	1.8×10^{-10}
Ab3.H	9.4×10^{5}	1.6×10^{-5}	1.7×10^{-11}
Ab4.H	1.0×10^{6}	1.3×10^{-4}	1.3×10^{-10}
Ab6.H	8.9×10^{5}	2.6×10^{-5}	2.9×10^{-11}
Ab7.H	1.0×10^{6}	5.2×10^{-5}	5.2×10^{-11}
Ab7A.H	1.0×10^{6}	6.0×10^{-5}	6.0×10^{-11}
Ab10.H	1.0×10^{6}	1.7×10^{-5}	1.7×10^{-11}
Ab11.H	6.4×10^{5}	1.4×10^{-5}	2.2×10^{-11}
Ab11A.H	7.4×10^{5}	6.0×10^{-5}	8.2×10^{-11}
Ab12.H	3.7×10^{5}	5.6×10^{-5}	1.5×10^{-10}

[1807] Examples of antibody affinities for CLIP are listed in Table 5.

[1808] TABLE 5.

Antibody	**Ka (1/Ms)**	**Kd (1/s)**	**K_D (M)**
Ab1	6.2×10^{5}	9.2×10^{-2}	1.5×10^{-7}
Ab2	8.4×10^{5}	2.6×10^{-2}	3.1×10^{-8}
Ab3	3.4×10^{5}	8.5×10^{-3}	2.5×10^{-8}
Ab4	7.1×10^{5}	1.9×10^{-1}	2.7×10^{-7}
Ab5	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab6	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$

Ab7	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab9	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab10	1.1×10^{6}	2.7×10^{-1}	2.5×10^{-7}
Ab11	1.6×10^{6}	8.6×10^{-2}	5.4×10^{-8}
Ab12	8.9×10^{5}	2.4×10^{-2}	2.7×10^{-8}
Ab1.H	5.8×10^{5}	1.2×10^{-2}	2.0×10^{-8}
Ab2.H	6.0×10^{5}	1.7×10^{-2}	2.8×10^{-8}
Ab3.H	3.2×10^{5}	5.3×10^{-3}	1.6×10^{-8}
Ab4.H	2.5×10^{5}	2.3×10^{-2}	9.2×10^{-8}
Ab6.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab7.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab7A.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab10.H	5.4×10^{5}	7.0×10^{-3}	1.3×10^{-8}
Ab11.H	5.4×10^{5}	1.1×10^{-2}	2.0×10^{-8}
Ab11A.H	7.0×10^{5}	1.4×10^{-2}	2.0×10^{-8}
Ab12.H	5.8×10^{5}	5.1×10^{-3}	8.8×10^{-9}

[1809] Examples of antibody affinities for alpha-MSH are listed in Table 6.

[1810] TABLE 6.

Antibody	**Ka (1/Ms)**	**Kd (1/s)**	**K_D (M)**
Ab1	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab2	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab3	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab4	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab5	2.6×10^{5}	1.4×10^{-2}	5.5×10^{-8}
Ab6	3.3×10^{5}	5.2×10^{-3}	1.6×10^{-8}
Ab7	1.3×10^{5}	1.3×10^{-2}	5.4×10^{-8}
Ab9	9.0×10^{5}	9.0×10^{-3}	6.3×10^{-8}

Ab10	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab11	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab12	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab1.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab2.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab3.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab4.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab6.H	2.4×10^{5}	4.0×10^{-3}	1.6×10^{-8}
Ab7.H	2.5×10^{5}	9.4×10^{-3}	3.7×10^{-8}
Ab7A.H	2.7×10^{5}	1.3×10^{-2}	4.8×10^{-8}
Ab10.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab11.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab11A.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$
Ab12.H	$<1.0 \times 10^{0}$	$>1.0 \times 10^{-1}$	$>1.0 \times 10^{-1}$

[1811] ***Example 3 Inhibition of ACTH-induced signaling via MC1R***

[1812] CHO-K1 cells expressing MC1R with a beta-lactamase reporter gene under the control of a cAMP response element (Life Technologies) were used in a GeneBLAzer® FRET cell based assay. Cells were grown in DMEM supplemented with 10% dialyzed FBS, 10mM glutamax, 0.1mM non-essential amino acids, 25mM HEPES, and 600ug/ml Hygromycin. The day before the assay the cells were detached with 0.25% trypsin, counted using a hemacytometer and adjusted to $2x10^{5}$ cells/ml in growth media. 100ul/well was plated in a 96-well black wall clear bottom plate. On the day of the assay anti-ACTH antibody dilutions starting at 40nM were incubated in the presence of 5nM ACTH (American Peptide) for 1hr at 37C. The media was removed from the MC1R cells and replaced with assay media alone, supplemented with ACTH, or ACTH incubated in the presence of the various antibody dilutions. All conditions were performed in duplicate. The cells were incubated for 4 hours and then loaded with 20µl 6x substrate loading solution (Life Technologies) for 2 hours and read at an excitation wavelength of 409nm and emission wavelengths 460 and 530nm. The ratio of blue (460nm) to green (530nm) was used for plotting.

[1813] Results

[1814] FIG. 18 is representative of the inhibition curves obtained by this method (results are shown for Ab1). The computed IC50 values for each antibody (shown in Table 7, below) demonstrate that Ab1-Ab7, Ab9-Ab12, Ab1.H-Ab7.H, Ab7A.H, Ab10.H-Ab12.H, and Ab11A.H inhibited ACTH-induced cAMP in cells expressing MC1R.

[1815] Table 7. Inhibition (IC50) of ACTH induced cAMP in cells expressing MC1R by anti-ACTH antibodies.

ANTIBODY	MC1R IC_{50} nM
Ab1	2.38
Ab2	3.62
Ab3	4.12
Ab4	5.73
Ab5	1.96
Ab6	1.04
Ab7	1.29
Ab9	1.32
Ab10	2.14
Ab11	1.49
Ab12	1.66
Ab1.H	1.36
Ab2.H	2.67
Ab3.H	2.06
Ab4.H	2.27
Ab6.H	1.83
Ab7.H	1.64
Ab7A.H	1.19
Ab10.H	0.54
Ab11.H	1.37
Ab11A.H	0.95
Ab12.H	1.99

[1816] ***Example 4 Inhibition of ACTH-induced signaling via MC3R, MC4R and MC5R***

[1817] Methods

[1818] For Ab1-Ab7 and Ab9, CHO-K1 cells expressing MC3R, MC4R or MC5R with a reporter gene under the control of a cAMP response element (Life Technologies) were used in a Meso Scale Discovery assay measuring cAMP. Cells were grown in DMEM supplemented with 10% dialyzed FBS, 10mM glutamax, 0.1mM non-essential amino acids, 25mM HEPES, 5μg/ml blasticidin and 600μg/ml Hygromycin (MC3R), 100μg/ml Zeocin (MC4R) or 400μg/ml Hygromycin (MC5R). The day of the assay the cells were detached with 5mM EDTA, counted using a hemacytometer and

adjusted to $2x10^6$ cells/ml in Hepes buffered saline plus MgCl2, pH 7.3 (assay buffer). A 1:2 dilution series of anti-ACTH antibodies were incubated in the presence of ACTH (American Peptide or Bachem) for 1 hour at 37°C. For MC3R and MC4R, antibody concentrations started at 833nM and ACTH was used at 100nM. For MC5R, antibody concentrations started at 17μM and ACTH was used at 5μM. Twenty microliters of the assay buffer, ACTH or antibody/ACTH mixture was then added to the assay plate, followed by 10μl of cells. After a 30 minute incubation at room temperature with shaking, the cells were lysed with 20μl assay buffer plus Triton X-100 supplemented with 2.5nM TAG-cAMP for 1 hour at room temperature with shaking. Finally 100μl of 1.5x Read buffer T was added to each well and read on a Sector Imager 2400.

[1819] For Ab10-Ab12, Ab1.H-Ab7.H, Ab7A.H, Ab10.H-Ab12.H, and Ab11A.H, to identify antibodies that neutralize ACTH 1-39 induced signaling via MC3R or MC4R, antibody solutions were incubated with ACTH (1-39) at 4x the final concentration (250nM) for 1hr. While the antibody/antigen complexes were incubated for 1 hour, MC3R or MC4R cells (Life Technologies) were detached with 0.25% trypsin for 4 minutes. The cells were washed and re-suspended at $1x10^6$ cells per ml culture media. Twenty microliters of Ab/antigen mixture was mixed with 20μl of cells in HTRF plates and incubated with shaking for 30 minutes. Twenty microliters of Eu3+ cryptate labeled anti-cAMP MAb and 20μl d2-labeled cAMP was added to each well and incubated for 1 hour with shaking. Fluorescence was measured at 620 and 665nM with a delay of 300 μsec.

[1820] Also for Ab10-Ab12, Ab1.H-Ab7.H, Ab7A.H, Ab10.H-Ab12.H, and Ab11A.H, to identify antibodies that neutralize ACTH 1-39 induced signaling via MC5R, antibody solutions were incubated with ACTH (1-39) at 4x the final concentration (10uM) for 1hr. While the antibody/antigen complexes were incubated for 1 hour, MC5R cells (Life Technologies) were detached with 0.25% trypsin for 4 minutes. The cells were washed and re-suspended at $1x10^6$ cells per ml culture media. Twenty microliters of Ab/antigen mixture was mixed with 20μl of cells in HTRF plates and incubated with shaking for 30 minutes. Twenty microliters of Eu3+ cryptate labeled anti-cAMP MAb and 20μl d2-labeled cAMP was added to each well and incubated for 1 hour with shaking. Fluorescence was measured at 620 and 665nM with a delay of 300 μsec.

[1821] Results

[1822] FIGs. 19, 20, and 21 are representative of the observed antibody inhibition of ACTH induced cAMP in cells expressing MC3R, MC4R, and MC5R respectively (results are shown for Ab1). The computed IC50 values for each antibody (shown in Table 8, below) demonstrate that Ab1-Ab7, Ab9-Ab12, Ab1.H-Ab7.H, Ab7A.H, Ab10.H-Ab12.H, and Ab11A.H inhibited ACTH-induced cAMP in cells expressing MC3R, MC4R, and MC5R.

[1823] Table 8. Inhibition (IC50) of ACTH induced cAMP in cells expressing MC3R, MC4R, and MC5R by anti-ACTH antibodies.

ANTIBODY	MC3R IC_{50} nM	MC4R IC_{50} nM	MC5R IC_{50} µM
Ab1	101.0	56.4	1.1
Ab2	79.0	54.5	1.1
Ab3	58.7	54.2	1.1
Ab4	113.0	65.8	1.3
Ab5	58.1	43.4	1.0
Ab6	62.8	55.2	1.0
Ab7	64.2	49.7	1.1
Ab9	55.7	50.6	1.1
Ab10	133.2	66.3	5.4
Ab11	108.3	49.4	4.2
Ab12	99.7	50.6	5.4
Ab1.H	83.9	43.7	3.6
Ab2.H	65.6	46.3	2.4
Ab3.H	70.6	34.8	3.5
Ab4.H	87.7	41.8	3.1
Ab6.H	89.6	52.2	3.9
Ab7.H	94.4	49.3	4.7
Ab7A.H	92.3	55.9	not determined
Ab10.H	104.3	50.6	3.5
Ab11.H	57.8	33.8	3.8
Ab11A.H	59.1	35.9	3.1
Ab12.H	78.2	46.9	3.7

[1824] ***Example 5 Inhibition of ACTH-induced cortisol secretion by Y1 cells***

[1825] The Y-1 cell line (mouse adrenal cell line) (ATCC) secretes cortisol in response to ACTH stimulation. Cells were grown on collagen coated flasks in Ham's F-12K media supplemented with 15% Horse Serum and 2.5% FBS. Cells at 400,000 cells/ml were seeded at 100µl per well into a collagen coated clear bottom black walled 96 well plate (Costar) and incubated overnight. The media was then changed to F12K supplemented with 1% BSA (assay media) and cells incubated overnight. Assay media supplemented with 3nM ACTH (American Peptide or Bachem) was incubated in the presence of anti-ACTH antibody (1:3 dilution series starting at 81nM) at 37°C for 1 hour. The media was removed from the Y-1 cells and replaced with assay media alone, supplemented with ACTH, or ACTH incubated in the presence of the various antibodies. Treatment of the cells was for 24hrs. The experimental media was removed from cells, diluted 1:10 and the cortisol level was determined with Cortisol parameter assay kit (R&D, Minneapolis, MN). Briefly microplate strips were incubated with 50µl Primary Antibody solution (except non-standard binding wells) for 1 hour at room temperature with shaking. Plate was then washed 4x with 400µl/well wash buffer. Then 100µl standards and

samples were added to the plate, followed by 50µl cortisol conjugate. Plates were incubated 2 hours at room temperature with shaking and then washed as above. The plates were developed with 200µl/well substrate solution for 30 minutes, followed by the addition of 50µl/well stop solution. Plates were read at 450nm with a 570nm correction.

[1826] Results

[1827] FIG. 22 is representative of the observed antibody inhibition of ACTH induced cAMP in Y1 cells (results are shown for Ab1). The computed IC50 values for each antibody (shown in Table 9, below) demonstrate that Ab1-Ab7, Ab9-Ab12, Ab1.H-Ab7.H, Ab7A.H, Ab10.H-Ab12.H, and Ab11A.H inhibited ACTH-induced cortisol in Y1 cells.

[1828] Table 9. Inhibition (IC50) of ACTH induced cortisol in Y1 cells by anti-ACTH antibodies.

ANTIBODY	Y1 Cells IC_{50} nM
Ab1	2.36
Ab2	2.35
Ab3	7.72
Ab4	17.19
Ab5	3.49
Ab6	1.44
Ab7	2.49
Ab9	3.47
Ab10	5.98
Ab11	1.53
Ab12	2.68
Ab1.H	1.77
Ab2.H	1.96
Ab3.H	4.04
Ab4.H	2.43
Ab6.H	1.62
Ab7.H	2.05
Ab7A.H	2.26
Ab10.H	1.06
Ab11.H	0.97
Ab11A.H	2.53
Ab12.H	4.13

[1829] ***Example 6 Reduction of corticosterone levels in mice by anti-ACTH antibodies***

[1830] A pharmacodynamics study was conducted in female C57BL/6 mice. Five mice were injected with buffer and groups of 10 mice were dosed with either 10mg/kg of a control antibody of

the same isotype (AD26-10), Ab2 or Ab3. Injections were performed by IV (tail vein) bolus administration on days 1 and day 7.

[1831] Blood samples were collected 24 hours before injection of test article (day 0), day 3, day 9 and day 12 in K_3EDTA tubes and processed to plasma for corticosterone analysis. All samples were stored at -70°C.

[1832] Corticosterone levels in mouse plasma samples were assessed using a Corticosterone EIA kit (Enzo Life Sciences) according to manufacturer's protocol. Briefly 100µl plasma samples are diluted 1:20, standards and controls were added to assay plate, followed by 50µl of an alkaline phosphatase conjugated corticosterone and 50µl of a polyclonal Ab to corticosterone. Assay plate was incubated 2 hours at room temperature with shaking and then washed. It was developed with p-Npp for 1 hour and then read at 405 with a 570nm subtraction.

[1833] Results: FIGs. 23-26 demonstrate that Ab2 and Ab3 decrease plasma corticosterone levels in mice. Corticosterone remained at detectable levels but was significantly reduced in all samples after anti-ACTH antibody injection.

[1834] ***Example 7 Reduction of corticosterone levels in rats by anti-ACTH antibodies***

[1835] A pharmacodynamics study was conducted in male Lewis rats. On day 1, rats were implanted with an Alzet pump (Durect #2ML1, 10ul/hr for 7 days) delivering either vehicle or rat ACTH (Bachem) at a rate of 0.05mg/kg/day. Twenty-four hours after pump implantation, the rats were injected with either 10mg/kg of a control isotype antibody (AD26-10) or Ab6. Injections were performed by IV (tail vein) bolus administration. The study was terminated 6 days post antibody injection.

[1836] Body weights were recorded daily and blood samples were collected on day 0, 2, 3, 5, 7, and 8 in K_3EDTA tubes and processed to plasma for corticosterone and aldosterone analysis. All samples were stored at -70°C.

[1837] Corticosterone levels in rat plasma samples were assessed using a Corticosterone EIA kit (Enzo Life Sciences) according to manufacturer's protocol. Briefly 100µl plasma samples were diluted 1:20, standards and controls were added to assay plate, followed by 50µl of an alkaline phosphatase conjugated corticosterone and 50µl of a polyclonal Ab to corticosterone. The assay plate was incubated 2 hours at room temperature with shaking and then washed. It was developed with p-Npp for 1 hour, then stopped and read at 405 with a 570nm subtraction.

[1838] Results

[1839] FIG. 27 demonstrates Ab6 inhibited ACTH induced weight loss. A one-way analysis of variance (ANOVA) was performed. Plasma corticosterone and aldosterone levels at day 0 (before antibody administration or pump implantation) are shown in FIG. 28 and FIG. 34, respectively. Plasma corticosterone and aldosterone levels at day 2 (24 hours post pump implantation but pre-Ab

dosing) are shown in FIG. 29 and FIG. 35, respectively. The results show that Ab6 reduced corticosterone (FIGs. 30-33) and aldosterone (FIGs. 36-39) levels at days 3, 5, 7, and 8, with statistically significant reductions observed in both corticosterone and aldosterone at days 3, 5, and 7, and at day 8 for aldosterone. A Mann-Whitney two-tailed P value analysis was performed comparing groups to the ACTH/AD26-10 group. Statistical significance values are as shown in the figures.

[1840] It was observed in some experiments that corticosterone levels varied from day to day, which was thought to result from varying levels of stress, e.g., as a result of handling the animals. Notwithstanding, consistent differences were observed between the control and treatment groups (as well as statistically significant differences between them), indicating effectiveness of the antibody at neutralizing ACTH activity *in vivo*. As in the mouse experiments, corticosterone remained at detectable levels but was significantly reduced in all samples after anti-ACTH antibody injection.

[1841] ***Example 8***

[1842] Epitope mapping of Anti-ACTH Antibodies

[1843] ACTH peptides were synthesized with a single point mutation in each position replacing the native amino acid with an Alanine (Ala). In positions 27, 32 and 34 the native Ala was replaced with Valine (Val). Per the usual convention these mutants are identified by the position in ACTH 1-39 followed by the letter code for the substituted amino acid, e.g., 7A indicates ACTH 1-39 substituted with alanine at amino acid position 7. Binding of monoclonal antibodies for human ACTH and each mutant peptide was detected using Surface Plasmon Resonance (SPR) on the ProteOn™ XRP36 (Bio-Rad, Hercules, CA). Samples and sample controls were immobilized onto a GLC sensor chip at a single density using standard amine coupling. The running buffer for immobilization consisted of 1x HBS-EP+ (10mM HEPES, 150mM NaCl, 3mM EDTA, 0.05% Polysorbate 20, pH 7.6) and was carried out at 25 degrees C. The GLC chip was initialized and pre-conditioned per the manufacturer's protocol (bi-directional injections of 0.5% SDS, 50mM NaOH, 100mM HCl). The immobilization process was carried out step-wise to ensure a unique antibody on the spots of the ProteOn™ Chip. Activation of the surface was by a 1:1 mixture of EDAC/NHS and flow rate of 30uL/min x 6 minutes. Antibody samples were previously dialyzed or exchanged to 10mM HEPES 150mM NaCl pH 7.2 and the antibody concentration was quantified using a Nanodrop™2000 spectrophotometer (ThermoScientific). The immobilization targeted 2000-3000 RU. Antibody samples (10ug/mL) in 10mM Sodium Acetate, pH 5.5 were flowed at 30uL/min x 6 minutes. Deactivation was done at a flow rate of 30uL/min for 6 minutes using 0.5M Ethanolamine concomitantly with the next activation.

[1844] Following immobilization, the running buffer was changed to 1x HBS-EP+ with BSA (0.2mg/mL) (as a carrier) and Sodium Azide (4uM) (as a preservative) and the chip surface was allowed to re-equilibrate with an injection of new running buffer. Stock solutions of human ACTH

peptide (1-39) and alanine/valine mutant peptides (Molecular Weight(s): 4.5kD) at (1mg/mL) were added to the running buffer at concentrations of 0.45 μg/mL (100nM) and used to query individual spots on the chip surface with flow rates of 100uL/min x 2 minutes and allowed to dissociate for 1000 seconds. Regeneration of surfaces between analytes was accomplished with Glycine 10mM at pH 2.0. The tested antibodies were either the original rabbit sequence or humanized variants of each of the subject antibodies, specifically, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab5, Ab6.H, Ab7.H, Ab9, Ab10.H, Ab11.H, Ab11A.H, Ab12.H, where in each instance the appended ".H" indicates the humanized form of the identified antibody. Ab11A.H is a variant of Ab11.H containing a sequence difference within one of the CDRs, which was observed to cause a slight difference in epitope binding (one amino acid difference). Because the humanization process generally retains the binding specify of the antibody to the target the tested antibodies are interpreted to bind to the same epitopes as their respective parent antibodies.

[1845] Sensorgrams representing affinity data of mutant peptide binding to a panel of antibodies were assessed via multiple measures. A visual inspection was first performed for each sensorgram to assess apparent maximal response (Rmax) relative to the native ACTH peptide (1-39). Second, a visual inspection of the dissociation phase was performed with an emphasis on the curve shape relative to the native ACTH peptide. Off-rates were calculated for native ACTH peptide and binding of each mutant peptide to the panel of antibodies. Finally, to confirm the integrity of each peptide reagent, each member of the peptide library was individually assessed to a broad panel of antibodies to ensure each peptide displayed binding activity similar to the native peptide to at least one antibody. The determination of amino acids residues important for antibody binding were made based on the collective assessment of all parameters described.

[1846] Results

[1847] Binding and dissociation curves are shown in FIG. 40A-L for binding of antibodies Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab5, Ab6.H, Ab7.H, Ab9, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H, respectively. The upper panel shows the binding curves for positions important for antibody binding (labeled at the right end, e.g., "21A" indicates the binding curve for the alanine scan mutant containing Alanine at position 21). The lower panel shows the binding of the remaining mutant positions, i.e., those determined not to be important for antibody binding. For reference, both panels also show the binding curve for wild-type ACTH (labeled huACTH(1-39)).

[1848] FIG. 41 tabulates the effects of all of the ACTH mutants on antibody binding. The positions listed in each column identify the alanine scanning mutants that were determined to be important for antibody binding; these are shown in order of position in order to illustrate the spatial arrangement of the residues along the ACTH primary sequence. The positions important for antibody binding were interpreted to jointly make the epitopes bound by each antibody. Based on these results, the epitopes bound by each antibody were concluded to be as follows:

[1849] Ab1 or Ab1.H: epitope containing residues 16, 18, and 20-23 of human ACTH.

[1850] Ab2 or Ab2.H: epitope containing residues 16, 18, and 20-23 of human ACTH.

[1851] Ab3 or Ab3.H: epitope containing residues 16, 18, and 20-23 of human ACTH.

[1852] Ab4 or Ab4.H: epitope containing residues 16, 18, and 20-23 of human ACTH.

[1853] Ab5: epitope containing residues 7-11, 13-14, and 18-19 of human ACTH.

[1854] Ab6 or Ab6.H: epitope containing residues 7-11, 13-14, 16, 18-19, and 23 of human ACTH.

[1855] Ab7 or Ab7.H: epitope containing residues 7-11, 13-14, and 18-19 of human ACTH.

[1856] Ab9: epitope containing residues 7-11, 14, and 18 of human ACTH.

[1857] Ab10 or Ab10.H: epitope containing residues 16, 18, and 20-23 of human ACTH.

[1858] Ab11 or Ab11.H: epitope containing residues 16-18 and 20-23.

[1859] Ab11A.H: epitope containing residues 16-23 of human ACTH.

[1860] Ab12 or Ab12.H: epitope containing residues 16-23 of human ACTH.

[1861] From these results it was further noted that the antibodies can be divided into two groups based upon the amount of overlap between the residues forming the epitope. One group contains antibodies Ab1-Ab4, Ab10-Ab12, Ab1.H-Ab4.H, Ab10.H, Ab11.H, and Ab11A.H that each bind to residues 16, 18, and 20-23 of human ACTH, and optionally further bind to residues 17 and/or 19. The second group includes antibodies Ab5-Ab7, Ab6.H, Ab7.H, Ab7A.H, and Ab9 that each bind to residues 7-11, 14, and 18 of human ACTH, and optionally further bind to residues 13, 16, and/or 19. From these results it was concluded that an antibody that binds to the same epitope as any of these antibodies, or overlaps in binding with residues of either or both of these epitopes, would likely have similar biological activity as the subject antibodies, including the ability to block MCR activation and inhibit the release of cortisol and aldosterone *in vivo*. Additionally, antibodies that bind to these epitopes or a subset of residues thereof are predicted to resemble the subject antibodies in their binding affinity characteristics, including exhibiting stronger affinity for ACTH than for alpha-MSH or CLIP (such as at least 10-fold, at least 100-fold, or at least 1000-fold stronger affinity for human ACTH than for alpha-MSH or CLIP or for both alpha-MSH and CLIP, i.e., a numerically lower K_D for ACTH than for alpha-MSH or CLIP by at least 10-fold, at least 100-fold, or at least 1000-fold).

[1862] ***Example 9 Anti-ACTH Antibodies Inhibit binding of ACTH to MC2R***

[1863] Inhibition of ACTH binding to the melanocortin-2 receptor (MC2R) was determined using ACTH (1-39) 23 TYR, [125I] (Perkin Elmer) and an MC2R transfected cell line (Invitrogen). Briefly, MC2R cells were cultured to logarithmic growth in DMEM containing 10% dialyzed FBS, L-glutamine, NEAA, and HEPES. Selection pressure for MC2R expression was maintained on the cells using Blasticidin, Zeocin, and Hygromycin at 5, 100, and 600 µg/ml, respectively. Cells were harvested and plated on Perkin Elmer Cytostar-T™ Scintillating Microplates at $4x10^4$ cells/well in

100 µL of media and incubated at 35-38°C in 5% CO_2 for 18-24 hours. Following incubation cells were aspirated of media and 100 µL of DMEM containing 2% BSA (DMEM-BSA) was added to each well. Cells were incubated until the treatment solution was prepared.

[1864] The ^{125}I-ACTH tracer solution was prepared by adding 40 µL of the ACTH (1-39) 23 TYR, [125I] to 10 ml of DMEM-BSA (final concentration with cell 6.4pM). Each antibody to be evaluated was prepared as a 1 mg/ml intermediate stock in DMEM-BSA from a 5 mg/ml master stock. Each antibody solution (20 µl) and ^{125}I-ACTH tracer (480 µl) were combined and incubated for 30 minutes at 35-38°C. Cells were aspirated and incubated in the presence of ^{125}I-ACTH tracer (Max binding), ^{125}I-ACTH tracer + antibody, or ^{125}I-ACTH tracer + ACTH, 1 µM (ACTH control) for 1 hour at 35-38°C in 5% CO_2. Nonspecific background binding was determined by adding the ^{125}I-ACTH tracer to cell-free wells (Background). At the end of incubation period wells were analyzed for ^{125}I-ACTH tracer binding using a MicroBeta® Trilux (Perkin Elmer) to determine the calculated counts per minute of each well.

[1865] Results

[1866] FIG. 42 shows that all anti-ACTH antibodies completely inhibited ACTH binding to MC2R (similar to the background level measured in the absence of cells, which is shown in the second bar from the left) within the limits of detection of the assay. As expected, three negative control antibodies (three rightmost bars) fail to inhibit ACTH binding as indicated by similar to levels detected in the absence of antibody (leftmost bar). The third to fourteenth columns from left to right in the bar graph correspond to the results for the tested antibodies.

[1867] These results indicate that the mechanism by which the subject anti-ACTH antibodies inhibit activation of MC2R is by preventing binding of ACTH to this receptor. From these results it is predicted that activation of the other MCRs (MC1R, MC3R, MC4R, and MC5R) is by a similar mechanism, i.e., by decreasing or abolishing ACTH binding to the MCRs.

[1868] ***Example 10. Recognition of ACTH 1-24 by Recombinant Antibodies by ELISA.***

[1869] ACTH is a 39 amino acid peptide but analyses of various truncated ACTH peptides have demonstrated ACTH 1-24 has full agonist activity of MC2R (Chen et al., *Biochemistry* 2007; 46 (40): 11389-11397). The peptide sequence of ACTH 1-24 is fully conserved (100% identity) among mammalian species including human (SEQ ID NO:882), horse (Equus przewalskii , NCBI Accession No. XP_008513480), cat (Felis catus, NCBI Accession No. XP_003984482), and dog (canus lupus familiaris, NCBI accession no. AAK08973). In Example 9, above, it was demonstrated that each of the tested antibodies recognized ACTH epitopes exclusively contained in ACTH 1-24. Additionally, Ab1-Ab7 and Ab9 bind ACTH 1-24 with similar affinity to ACTH 1-39 (data not shown). Taken together, these results strongly suggest that the subject anti-ACTH antibodies would be able to bind to the conserved ACTH 1-24 sequence within of horse, dog, and cat ACTH and thereby inhibit

biological activities of ACTH in these species. This was further assessed by determining whether the anti-ACTH antibodies could block MC2R receptor activation by the ACTH 1-24 peptide sequence that is 100% conserved among humans, horses, dogs, and cats.

[1870] Methods

[1871] To assess neutralization of ACTH 1-24 induced signaling via MC2R, antibody solutions were incubated with ACTH (1-24) at 4x the final concentration (600pM) for 1hr. While the antibody/antigen complexes were incubated for 1 hour, MC2R cells (Life Technologies) were detached with 0.25% trypsin for 4 minutes. The cells were washed and re-suspended at 1x106 cells per ml culture media. Twenty microliters of Ab/antigen mixture was mixed with 20µl of cells in HTRF plates and incubated with shaking for 30 minutes. Twenty microliters of Eu3+ cryptate labeled anti-cAMP MAb and 20µl d2-labeled cAMP was added to each well and incubated for 1 hour with shaking. Fluorescence was measured at 620 and 665nM with a delay of 300 µsec.

[1872] Results

[1873] FIG. 43 shows an inhibition curve (for Ab2) that is representative of the inhibition curves obtained with the other tested antibodies. The inhibition results were quantified for each antibody to yield an IC50 value, which are summarized in Table 10 below. These results demonstrated that anti-ACTH antibodies Ab2, Ab2.H,Ab3, Ab3.H, Ab6, and Ab6.H inhibited ACTH 1-24 induced cAMP in cells expressing MC2R. Notably, the antibodies tested were representative of the two different epitope groups identified in Example 9, indicating that the antibodies of either group would have similar therapeutic activity in veterinary applications.

[1874] Table 10. IC50 (nM) for antibody inhibition of MC2R receptor activation by the ACTH 1-24 peptide.

Antibody	IC50 (nM)
Ab2	1.3
Ab2.H	0.6
Ab3	0.8
Ab3.H	0.4
Ab6	0.1
Ab6.H	0.1

[1875] ***Example 11. Yeast Cell Expression***

[1876] Construction of Pichia pastoris expression vectors for heavy and light chain.

[1877] The humanized variable light and heavy chain fragments were amplified from the mammalian expression vectors using PCR and subcloned into a pGAP expression vector. The pGAP expression vector uses the GAP promoter to drive expression of the immunoglobulin chain and a secretion leader sequence for export. In addition, this vector contains common elements such as a bacterial origin of replication, and a copy of an antibiotic resistance gene for selection of

transformants that contain the desired expression vector integrated into their genome. For the vectors targeting integration into the GAP promoter locus of the P. pastoris genome, the pGAP vector carries an expression cassette for the kanamycin resistance gene which confers resistance to the antibiotic G418. For the vector targeting integration into the HIS4 TT locus of the P. pastoris genome, the pGAP vector carries an expression cassette for the Sh ble gene that permits selection of transformants with the antibiotic Zeocin.

[1878] Transformation of expression vectors into haploid met1 and lys3 host strains of Pichia pastoris

[1879] All methods used for transformation of haploid P. pastoris strains were done as described in Lin-Cereghino et al., *Biotechniques*. 2005 Jan;38(1):44, 46, 48. Prior to transformation each vector was linearized within the GAP promoter sequences to direct the integration of the vector into the GAP promoter locus of the P. pastoris genome. Haploid strains were transfected using electroporation and successful transformants were selected on YPDS (yeast extract, peptone dextrose with sorbitol) G418 agar plates. Copy numbers of heavy and light chain genes were determined for haploid strains by Southern blot analysis. Dual locus strains were generated using the methods disclosed in U.S. Pre-Grant Patent Publication No. 2013/0045888, the contents of which are incorporated by reference in its entirety. Briefly, a haploid containing two copies of the heavy chain expression vector integrated at pGAP was identified and retransformed with a heavy chain expression vector targeting integration into the HIS4 TT locus. Transformants containing copies of heavy chain expression vectors integrated at both the GAP promoter and HIS4 TT loci were selected on YPDS plates containing G418 and Zeocin. Haploid strains were then mated and selected for their ability to grow in the absence of the amino acid markers (i.e., Lys and Met). Resulting diploid clones were then subjected to a final Southern blot to confirm copy numbers of heavy and light chain genes. A clone expressing the antibody of interest was characterized using biolayer interferometry Protein-A biosensors to monitor expression (Octet, ForteBio).

[1880] ***Example 12. Expression of Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab11.H, Ab11A.H, and Ab12.H in Pichia pastoris.***

[1881] Pichia strains for expression of full-length antibody were made. For all the full length antibody expressing strains, haploids strains were created and subsequently mated. One haploid strain expressed full-length light chain sequence and another haploid strain expressed the full-length heavy chain sequence. Each diploid strain was used to generate a research cell bank and used for expression in a bioreactor.

[1882] First an inoculum was expanded using the research cell bank using medium comprised of the following nutrients (%w/v): yeast extract 3%, glycerol 2%, YNB 1.34%, Biotin 0.004% and 200 mM potassium phosphate. To generate the inoculum for the fermenters, the cell bank was expanded

for approximately 29 hours in a shaking incubator at 30 °C and 300 RPM. A 10% inoculum was then added to Labfors 2.5L working volume vessels containing 1 L sterile growth medium. The growth medium was comprised of the following nutrients: potassium sulfate 18.2 g/L, ammonium phosphate monobasic 35.6 g/L, potassium phosphate dibasic 12.8 g/L, magnesium sulfate heptahydrate 3.72 g/L, sodium citrate dihydrate 10 g/L, glycerol 40 g/L, yeast extract 30 g/L, PTM1 trace metals 4.35 mL/L, and antifoam 204 1.67 mL/L. The PTM1 trace metal solution was comprised of the following components: cupric sulfate pentahydrate 6 g/L, sodium iodide 0.08 g/L, manganese sulfate hydrate 3 g/L, sodium molybdate dehydrate 0.2 g/L, boric acid 0.02 g/L, cobalt chloride 0.5 g/L, zinc chloride 20 g/L, ferrous sulfate heptahydrate 65 g/L, biotin 0.2 g/L, and sulfuric acid 5 mL/L.

[1883] The bioreactor process control parameters were set as follows: Agitation 1,000 RPM, airflow 1.35 standard liter per minute, temperature 28 °C and pH was controlled at six using ammonium hydroxide. No oxygen supplementation was provided.

[1884] Fermentation cultures were grown for approximately 12 to 16 hours until the initial glycerol was consumed as denoted by a dissolved oxygen spike. Immediately following the dissolved oxygen spike, a bolus addition of ethanol was added to the reactor to reach 1% ethanol (w/v). The fermentation cultures were allowed to equilibrate for 15 to 30 minutes. Feed addition was initiated 30 minutes post-ethanol bolus and set at a constant rate of 0.5 mL/min for 40 minutes, then the feed pump was controlled by an ethanol sensor keeping the concentration of ethanol at 1% for the remainder of the run using an ethanol sensing probe (Raven Biotech). The feed was comprised of the following components: yeast extract 50 g/L, anhydrous dextrose 500 g/L, sodium citrate dehydrate 0.5 g/L and PTM1 trace metals 12 mL/L. The total fermentation time was approximately 86 hours.

[1885] ***Example 13. Reduction of corticosterone levels in rats by anti-ACTH antibodies***

[1886] A pharmacodynamics study was conduced in male Lewis rats. On day 1, rats were implanted with an Alzet pump (Durect #2ML1, 10ul/hr for 8 days) delivering either vehicle or rat ACTH (Bachem) at a rate of 0.05mg/kg/day. Twenty-four hours later the rats were injected with either 10mg/kg of a control isotype antibody (AD26-10) or Ab1.H. Injections were performed by IV (tail vein) bolus administration. The study was terminated 8 days post antibody injection.

[1887] Body weights were recorded daily and blood samples were collected on day 0, 2, 3, 5, 7, and 8 in K_3EDTA tubes and processed to plasma for corticosterone and aldosterone analysis. All samples were stored at -70°C.

[1888] Corticosterone levels in rat plasma samples were assessed using a Corticosterone EIA kit (Enzo Life Sciences) according to the manufacturer's protocol. Briefly, 100µl plasma samples were diluted 1:20, standards and controls were added to the assay plate, followed by 50µl of an alkaline phosphatase conjugated corticosterone and 50µl of a polyclonal Ab to corticosterone. The assay plate

was incubated 2 hours at room temperature with shaking and then washed. It was developed with p-Npp for 1 hour, then stopped and read at 405 with a 570nm subtraction.

[1889] Aldosterone levels in rat plasma samples were assessed using an aldosterone EIA kit (Enzo Life Sciences) according to the manufacturer's protocol. Briefly, 100µl plasma samples were diluted 1:10, standards and controls were added to the assay plate, followed by 50µl of an alkaline phosphatase conjugated aldosterone and 50µl of a polyclonal Ab to aldosterone. The assay plate was incubated 16-24 hours at 4C and then washed. It was developed with p-Npp for 1 hour, then stopped and read at 405 with a 570nm subtraction.

[1890] Results

[1891] FIGS. 44-56 show the effects of Ab1.H on changes in body weight, plasma corticosterone, and plasma aldosterone levels that resulted from ACTH dosing. FIG. 44 shows the percentage change in animal weight by day over the course of the study, and shows that Ab1.H inhibited ACTH-induced weight loss. FIGs. 45 and 51 respectively show plasma corticosterone and aldosterone levels before ACTH and antibody dosing. FIGs. 46 and 52 respectively show plasma corticosterone and aldosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration. FIGs. 47 and 53 respectively show plasma corticosterone and aldosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration. FIGs. 48 and 54 respectively show plasma corticosterone and aldosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration. FIGs. 49 and 55 respectively show plasma corticosterone and aldosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration. FIGs. 50 and 56 respectively show plasma corticosterone and aldosterone levels 168 hours after initiation of ACTH dosing and 144 hours after the antibody administration. The results of statistical comparison between treatment groups at the varying time points are as indicated in the figures, and indicate statistically significant decreases in corticosterone and aldosterone caused by Ab1.H in the ACTH treatment group relative to animals treated with the isotype control, as well as statistically significant increases in corticosterone and aldosterone caused by ACTH dosing relative to vehicle-treated controls.

[1892] Overall, FIGS. 44-56 demonstrate that Ab1.H reduced corticosterone and aldosterone levels, and inhibited ACTH-induced weight loss.

[1893] ***EXAMPLE 14. Reduction of corticosterone levels in rats by anti-ACTH antibodies.***

[1894] A pharmacodynamics study was conduced in male Lewis rats. On day 1, rats were implanted with an Alzet pump (Durect #2ML1, 10ul/hr for 7 days) delivering either vehicle or rat ACTH (Bachem) at a rate of 0.05mg/kg/day. Twenty-fours hours later the rats were injected with either 10mg/kg of a control antibody of the same isotype (AD26-10), Ab7A.H Ab10.H, Ab11.H,

Ab12.H, Ab11A.H, or with Ab2.H at 100mg/kg Injections were performed by IV (tail vein) bolus administration. The study was terminated 7 days post antibody injection.

[1895] Body weights were recorded daily and blood samples were collected on day 0, 2, 3, 5, and 7 in K_3EDTA tubes and processed to plasma for corticosterone and aldosterone analysis. All samples were stored at -70°C.

[1896] Corticosterone levels in rat plasma samples were assessed using a Corticosterone EIA kit (Enzo Life Sciences) according to manufacturer's protocol. Briefly 100µl plasma samples were diluted 1:100, standards and controls were added to assay plate, followed by 50µl of an alkaline phosphatase conjugated corticosterone and 50µl of a polyclonal Ab to corticosterone. The assay plate was incubated 2 hours at room temperature with shaking and then washed. It was developed with p-Npp for 1 hour, then stopped and read at 405 with a 570nm subtraction.

[1897] Aldosterone levels in rat plasma samples were assessed using an aldosterone EIA kit (Enzo Life Sciences) according to the manufacturer's protocol. Briefly, 100µl plasma samples were diluted 1:10, standards and controls were added to the assay plate, followed by 50µl of an alkaline phosphatase conjugated aldosterone and 50µl of a polyclonal Ab to aldosterone. The assay plate was incubated 16-24 hours at 4C and then washed. It was developed with p-Npp for 1 hour, then stopped and read at 405 with a 570nm subtraction.

[1898] Results

[1899] FIGS. 57-67 show the effects of Ab2.H, Ab11.H, and Ab12.H on changes in body weight, plasma corticosterone, and plasma aldosterone levels that resulted from ACTH dosing. FIG. 57 shows the percentage change in animal weight by day over the course of the study, and shows that Ab2.H, Ab11.H, and Ab12.H inhibited ACTH-induced weight loss. FIGs. 58 and 63 respectively show plasma corticosterone and aldosterone levels before ACTH and antibody dosing. FIGs. 59 and 64 respectively show plasma corticosterone and aldosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration. FIGs. 60 and 65 respectively show plasma corticosterone and aldosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration. FIGs. 61 and 66 respectively show plasma corticosterone and aldosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration. FIGs. 62 and 67 respectively show plasma corticosterone and aldosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration. The results of statistical comparison between treatment groups at the varying time points are as indicated in the figures, and indicate statistically significant decreases in corticosterone and aldosterone caused by Ab2.H, Ab11.H, and Ab12.H in the ACTH treatment group relative to animals treated with the isotype control, as well as statistically significant increases in aldosterone caused by ACTH dosing relative to vehicle-treated controls.

[1900] Overall, FIGS. 57-67 demonstrate that Ab2.H, Ab11.H, and Ab12.H inhibited ACTH-induced weight loss and ACTH-induced increases in corticosterone and aldosterone levels.

[1901] FIGS. 68-78 show the effects of Ab10.H on changes in body weight, plasma corticosterone, and plasma aldosterone levels that resulted from ACTH dosing. FIG. 68 shows the percentage change in animal weight by day over the course of the study, and shows that Ab10.H inhibited ACTH-induced weight loss. FIGs. 69 and 74 respectively show plasma corticosterone and aldosterone levels before ACTH and antibody dosing. FIGs. 70 and 75 respectively show plasma corticosterone and aldosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration. FIGs. 71 and 76 respectively show plasma corticosterone and aldosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration. FIGs. 72 and 77 respectively show plasma corticosterone and aldosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration. FIGs. 73 and 78 respectively show plasma corticosterone and aldosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration. The results of statistical comparison between treatment groups at the varying time points are as indicated in the figures, and indicate statistically significant decreases in corticosterone and aldosterone caused by Ab10.H in the ACTH treatment group relative to animals treated with the isotype control, as well as statistically significant increases in corticosterone and aldosterone caused by ACTH dosing relative to vehicle-treated controls.

[1902] Overall, FIGS. 68-78 demonstrate that Ab10.H inhibited ACTH-induced weight loss and ACTH-induced increases in corticosterone and aldosterone levels.

[1903] FIGS. 79-89 show the effects of Ab7A.H on changes in body weight, plasma corticosterone, and plasma aldosterone levels that resulted from ACTH dosing. FIG. 79 shows the percentage change in animal weight by day over the course of the study, and shows that Ab7A.H inhibited ACTH-induced weight loss. FIGs. 80 and 85 respectively show plasma corticosterone and aldosterone levels before ACTH and antibody dosing. FIGs. 81 and 86 respectively show plasma corticosterone and aldosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration. FIGs. 82 and 87 respectively show plasma corticosterone and aldosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration. FIGs. 83 and 88 respectively show plasma corticosterone and aldosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration. FIGs. 84 and 89 respectively show plasma corticosterone and aldosterone levels 144 hours after initiation of ACTH dosing and 120 hours after the antibody administration. The results of statistical comparison between treatment groups at the varying time points are as indicated in the figures, and indicate statistically significant decreases in corticosterone caused by Ab7A.H in the ACTH treatment group relative to animals treated with the isotype control, as well as statistically significant increases in corticosterone caused by ACTH dosing relative to vehicle-treated controls.

[1904] Overall, FIGS. 79-89 demonstrate that Ab7A.H inhibited ACTH-induced weight loss and ACTH-induced increases in corticosterone and aldosterone levels.

[1905] FIGS. 90-93 show the effects of Ab11A.H on changes in plasma corticosterone levels that resulted from ACTH dosing. FIG. 90 shows plasma corticosterone levels before ACTH and antibody dosing. FIG. 91 shows plasma corticosterone levels at 24 hours after initiation of ACTH dosing and before the antibody administration. FIG. 92 shows plasma corticosterone levels 48 hours after initiation of ACTH dosing and 24 hours after the antibody administration. FIG. 93 shows plasma corticosterone levels 96 hours after initiation of ACTH dosing and 72 hours after the antibody administration. The results of statistical comparison between treatment groups at the varying time points are as indicated in the figures, and indicate statistically significant decreases in corticosterone caused by Ab11A.Hin the ACTH treatment group relative to animals treated with the isotype control, as well as statistically significant increases in corticosterone caused by ACTH dosing relative to vehicle-treated controls.

[1906] Overall, FIGS. 90-93 demonstrate that Ab11A.H inhibited ACTH-induced increases in corticosterone levels.

[1907] The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

[1908] These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

[1909] The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A human, humanized or chimerized anti-human adrenocorticotrophic hormone (ACTH) antibody or antibody fragment that specifically binds to at least one linear or conformational epitope bound by an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H and/or competes for binding to at least one linear or conformational epitope on human ACTH bound by an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

2. A human, humanized or chimerized anti-human adrenocorticotrophic hormone (ACTH) antibody or antibody fragment that specifically binds to an epitope on human ACTH selected from the group consisting of:

(i) at least one of residues 16, 18, and 20-23 of human ACTH;

(ii) at least one of residues 7-11, 14, and 18 of human ACTH;

(iii) at least one of residues 16-18 and 20-23 of human ACTH;

(iv) at least one of residues 16-23 of human ACTH;

(v) at least one of residues 7-11, 13-14, and 18-19 of human ACTH;

(vi) at least one of residues 7-11, 13-14, 16, 18-19, and 23 of human ACTH;

(vii) at least two of the residues of any one of (i)-(vi);

(viii) at least three of the residues of any one of (i)-(vi);

(ix) at least four of the residues of any one of (i)-(vi);

(x) at least five of the residues of any one of (i)-(vi);

(xi) at least six of the residues of any one of (i)-(vi);

(xii) at least seven of the residues of any one of (ii)-(vi);

(xiii) at least eight of the residues of any one of (iv)-(vi);

(xiv) at least nine of the residues of any one of (v)-(vi);

(xv) at least ten of the residues of (vi); or

(xvi) all 11 of the residues of (vi).

3. A human, humanized or chimerized anti-human ACTH antibody or antibody fragment, wherein optionally said antibody or fragment does not bind alpha-MSH or CLIP, or binds each of alpha-MSH and CLIP with a K_D (binding affinity) at least 10-fold, at least 100-fold, or at least 1000-fold weaker than the binding affinity of said antibody or fragment for human ACTH.

4. An anti-human ACTH antibody or antibody fragment comprising:

(i) at least 2, at least 3, at least 4, at least 5, or all 6 complementarity determining regions (CDRs) of an anti-human ACTH antibody selected from the group consisting of Ab1, Ab2, Ab3, Ab4,

Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H; and/or

(ii) a variable heavy chain having a polypeptide sequence at least 80% identical to a polypeptide selected from the group consisting of: SEQ ID NO: 2, 42, 82, 122, 162, 202, 242, 282, 322, 362, 402, 442, 482, 522, 562, 602, 642, 682, 722, 762, 802, and 842 or a heavy chain polypeptide having a sequence at least 80% identical to a polypeptide selected from the group consisting of: SEQ ID NO: 1, 41, 81, 121, 161, 201, 241, 281, 321, 361, 401, 441, 481, 521, 561, 601, 641, 681, 721, 761, 801, and 841; and/or

(iii) a variable light chain having a polypeptide sequence at least 80% identical to a polypeptide selected from the group consisting of: SEQ ID NO: 22, 62, 102, 142, 182, 222, 262, 302, 342, 382, 422, 462, 502, 542, 582, 622, 662, 702, 742, 782, 822, and 862, or comprises a light chain polypeptide having a sequence at least 80% identical to a polypeptide selected from the group consisting of: SEQ ID NO: 21, 61, 101, 141, 181, 221, 261, 301, 341, 381, 421, 461, 501, 541, 581, 621, 661, 701, 741, 781, 821, and 861,

wherein optionally said antibody or antibody fragment is human, humanized, or chimeric.

5. An anti-ACTH antibody comprising the heavy chain CDR1, CDR2, and CDR3 polypeptides of SEQ ID NO: 484; SEQ ID NO: 486; and SEQ ID NO: 488, and/or the light chain CDR1, CDR2, and CDR3 of SEQ ID NO: 504; SEQ ID NO: 506; and SEQ ID NO: 508.

6. The anti-human ACTH antibody of claim 5, which is humanized or chimeric.

7. The anti-human ACTH antibody of claim 5 or 6, which comprises a variable heavy chain having at least 90% identity to the polypeptide of SEQ ID NO: 482 and/or which comprises a variable light chain having at least 90% identity to the polypeptide of SEQ ID NO: 502, or comprises said variable light chain and said variable heavy chain.

8. The anti-human ACTH antibody of any one of claims 5-7, which comprises a heavy chain having at least 90% identity to the polypeptide of SEQ ID NO: 481 and/or which comprises a light chain having at least 90% identity to the polypeptide of SEQ ID NO: 501, or comprises said light chain and said heavy chain.

9. The anti-human ACTH antibody of claim 5, which comprises or consists of the variable heavy chain of SEQ ID NO: 482 and the variable light chain of SEQ ID NO: 502, or comprises or consists of the heavy chain of SEQ ID NO: 481 and the light chain of SEQ ID NO: 501.

10. The anti-human ACTH antibody or antibody fragment of any one of **claims 1-9**, wherein the antibody or antibody fragment:

(i) is selected from the group consisting of scFvs, camelbodies, nanobodies, IgNAR, Fab fragments, Fab' fragments, MetMab like antibodies, monovalent antibody fragments, and $F(ab')_2$ fragments; and/or

(ii) the antibody or antibody fragment substantially or entirely lacks N-glycosylation and/or O-glycosylation; and/or the antibody or antibody fragment comprises a human constant domain; and/or

(iii) the antibody comprise an IgG1, IgG2, IgG3, or IgG4 constant domain or a constant domain; and/or the antibody or antibody fragment comprises an Fc region that has been modified to alter at least one of effector function, half-life, proteolysis, or glycosylation; and/or the antibody comprises the heavy chain constant domain polypeptide of SEQ ID NO: 886, 887, or 888; and/or

(iv) the antibody or antibody fragment is directly or indirectly attached to a detectable label or therapeutic agent, effector moiety, chemical moiety, detectable moiety, fluorescent dye, enzyme, substrate, bioluminescent material, radioactive material, chemiluminescent moiety, functional moiety, or combination thereof; and/or

(v) said antibody specifically binds to ACTH of a non-human animal, wherein optionally said non-human animal is selected from the group consisting of dog, cat, and horse.

11. The anti-human ACTH antibody or antibody fragment of any one of **claims 1-10**, which:

(i) binds to human ACTH with a binding affinity (K_D) of less than or equal to $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M; and/or

(ii) which binds to human ACTH with an off-rate (k_d) of less than or equal to $5x10^{-4}$ s^{-1}, 10^{-4} s^{-1}, $5x10^{-5}$ s^{-1}, or 10^{-5} s^{-1}; and/or

(iii) which binds to human alpha-MSH, to human CLIP, or to human alpha-MSH and human CLIP with a binding affinity (K_D) at least 100-fold or at least 1000-fold weaker than the binding affinity (K_D) of said antibody for human ACTH; and/or

(iv) when administered to a human subject inhibits or neutralizes at least one biological effect elicited by human ACTH; and/or

(v) neutralizes or inhibits human ACTH binding to and/or activation of at least one of MC1R, MC2R, MC3R, MC4R or MC5R or any combination thereof; and/or

(vi) inhibits ACTH-induced cortisol, corticosterone and/or aldosterone secretion when administered to a human subject, wherein optionally said anti-human ACTH antibody or fragment may reduce plasma cortisol levels, and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels; and/or

(vii) when administered to a human subject, reduces plasma cortisol, aldosterone and/or corticosterone levels, wherein optionally said anti-human ACTH antibody or fragment may reduce plasma cortisol levels, and/or may not abolish plasma cortisol levels, and/or may reduce plasma corticosterone levels, and/or may not abolish plasma corticosterone levels; and/or

(viii) binds to human ACTH with a K_D that is less than about 100 nM, less than about 10 nM, less than about 1 nM, less than about 100 pM, less than about 50 pM, less than about 25 pM, less than about 1 pM, between about 10 pM and about 100 pM, or about 40 nM; and/or

(ix) has stronger affinity for human $ACTH_{1-39}$ as compared to human alpha-MSH or human CLIP and/or does not bind to human alpha-MSH and/or does not bind to human CLIP; and/or

(x) has a binding affinity (K_D) for human ACTH that is at least 10-fold, 100-fold, or 1000-fold stronger (i.e., numerically lower) than the affinity of said antibody or antibody fragment for human alpha-MSH and/or human CLIP; and/or

(xi) has a binding affinity (K_D) for human ACTH that is 1 nM or less, 0.1 nM or less, 0.05 nM or less, or 0.02 nM or less, a binding affinity for human alpha-MSH that is 10^{-6} M or greater, and a binding affinity for human CLIP that is 10^{-8} M or greater; and/or

(xii) has a binding affinity (K_D) for human ACTH that is 1 nM or less, 0.1 nM or less, 0.05 nM or less, or 0.02 nM or less, a binding affinity for human alpha-MSH that is 10^{-8} M or greater, and a binding affinity for human CLIP that is 10^{-6} M or greater; and/or

(xiii) has a binding affinity (K_D) for human ACTH that is 1 nM or less, 0.1 nM or less, 0.05 nM or less, or 0.02 nM or less, a binding affinity for human alpha-MSH that is at least 1000-fold weaker than said binding affinity for human ACTH, and a binding affinity for human CLIP that is at least 100-fold weaker than said binding affinity for human ACTH; and/or

(xiv) has a binding affinity (K_D) for human ACTH that is 1 nM or less, 0.1 nM or less, 0.05 nM or less, or 0.02 nM or less, a binding affinity for human alpha-MSH that is at least 100-fold weaker than said binding affinity for human ACTH, and a binding affinity for human CLIP that is at least 1000-fold weaker than said binding affinity for human ACTH.

12. The antibody or antibody fragment of any one of **claims 1-10**, which:

(i) binds to a non-human animal ACTH with a binding affinity (K_D) of less than or equal to $5x10^{-5}$ M, 10^{-5} M, $5x10^{-6}$ M, 10^{-6} M, $5x10^{-7}$ M, 10^{-7} M, $5x10^{-8}$ M, 10^{-8} M, $5x10^{-9}$ M, 10^{-9} M, $5x10^{-10}$ M, 10^{-10} M, $5x10^{-11}$ M, 10^{-11} M, $5x10^{-12}$ M, 10^{-12} M, $5x10^{-13}$ M, or 10^{-13} M; and/or

(ii) which binds to a non-human animal ACTH with an off-rate (k_d) of less than or equal to $5x10^{-4}$ s^{-1}, 10^{-4} s^{-1}, $5x10^{-5}$ s^{-1}, or 10^{-5} s^{-1}; and/or

(iii) which binds to a non-human animal alpha-MSH, to a non-human animal CLIP, or to a non-human animal alpha-MSH and a non-human animal CLIP with a binding affinity (K_D) at least 100-fold or at least 1000-fold weaker than the binding affinity (K_D) of said antibody for the ACTH of the same species; and/or

(iv) when administered to a non-human animal subject inhibits or neutralizes at least one biological effect elicited by the ACTH of said species; and/or

(v) neutralizes or inhibits a non-human animal ACTH binding to and/or activation of at least one of MC1R, MC2R, MC3R, MC4R or MC5R orthologs or homologs of said non-human animal or any combination thereof; and/or

(vi) inhibits ACTH-induced cortisol, corticosterone and/or aldosterone secretion when administered to a non-human animal subject, wherein optionally said anti-ACTH antibody or fragment may reduce plasma cortisol or corticosterone levels, and/or may not abolish plasma cortisol or corticosterone levels; and/or

(vii) when administered to a non-human animal subject, reduces plasma cortisol, aldosterone and/or corticosterone levels, wherein optionally said anti-ACTH antibody or fragment may reduce plasma cortisol or corticosterone levels, and/or may not abolish plasma cortisol or corticosterone levels; and/or

(viii) binds to a non-human animal ACTH with a K_D that is less than about 100 nM, less than about 10 nM, less than about 1 nM, less than about 100 pM, less than about 50 pM, less than about 25 pM, less than about 1 pM, between about 10 pM and about 100 pM, or about 40 nM; and/or

(ix) has stronger affinity for a non-human animal full length ACTH as compared to the alpha-MSH of the same species or the CLIP of the same species and/or does not bind to the alpha-MSH of the same species and/or does not bind to the CLIP of the same species; and/or

(x) has a binding affinity (K_D) for a non-human animal ACTH that is at least 10-fold, 100-fold, or 1000-fold stronger (i.e., numerically lower) than the affinity of said antibody or antibody fragment for alpha-MSH of the same species and/or CLIP of the same speices; and/or

(xi) has a binding affinity (K_D) for a non-human animal ACTH that is 1 nM or less, 0.1 nM or less, 0.05 nM or less, or 0.02 nM or less, a binding affinity for the alpha-MSH of the same species that is 10^{-6} M or greater, and a binding affinity for the CLIP of the same species that is 10^{-8} M or greater; and/or

(xii) has a binding affinity (K_D) for a non-human animal ACTH that is 1 nM or less, 0.1 nM or less, 0.05 nM or less, or 0.02 nM or less, a binding affinity for the alpha-MSH of the same species that is 10^{-8} M or greater, and a binding affinity for the CLIP of the same species that is 10^{-6} M or greater; and/or

(xiii) has a binding affinity (K_D) for a non-human animal ACTH that is 1 nM or less, 0.1 nM or less, 0.05 nM or less, or 0.02 nM or less, a binding affinity for the alpha-MSH of the same species that is at least 1000-fold weaker than said binding affinity for human ACTH, and a binding affinity for the CLIP of the same species that is at least 100-fold weaker than said binding affinity for the ACTH of said species; and/or

(xiv) has a binding affinity (K_D) for a non-human animal ACTH that is 1 nM or less, 0.1 nM or less, 0.05 nM or less, or 0.02 nM or less, a binding affinity for the alpha-MSH of the same species that is at least 100-fold weaker than said binding affinity for the ACTH of said species, and a binding

affinity for the CLIP of said species that is at least 1000-fold weaker than said binding affinity for the ACTH of said species, wherein optionally said species is dog, cat, or horse.

13. A composition suitable for therapeutic, prophylactic, or a diagnostic use comprising a therapeutically, prophylactically or diagnostically effective amount of at least one anti-human ACTH antibody or antibody fragment according to any one of **claims 1-12**, wherein optionally said composition: is suitable for subcutaneous administration, is suitable for intravenous administration, or is lyophilized; and optionally further comprises a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, another active agent.

14. An isolated nucleic acid sequence or nucleic acid sequences encoding an anti-human ACTH antibody or antibody fragment according to any one of **claims 1-12**, which optionally is contained in a vector or vectors, host cell, mammalian cell, bacterial cell, fungal cell, yeast cell, avian cell, insect cell, yeast cell of the genus is *Pichia*, yeast cell of the species *Pichia pastoris*.

15. A method of producing an anti-human ACTH antibody or antibody fragment comprising translating the nucleic acid or culturing host cell containing according to **claim 14** or under conditions that provide for expression of said antibody or antibody fragment, and optionally isolating or purifying said antibody or fragment.

16. A method for blocking, inhibiting or neutralizing one or more biological effects associated with ACTH comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment according to any one of **claims 1-12** or composition according to **claim 13**.

17. A method for treating or preventing a condition associated with ACTH, comprising administering an effective amount of an anti-ACTH antibody according to any one of claims 5-9 to a subject in need thereof.

18. The method of claim 17, wherein said condition associated with ACTH comprises Cushing's disease, Cushing's syndrome, hypertension, hyperaldosteronism, familial hyperaldosteronism, primary hyperaldosteronism, or secondary hyperaldosteronism.

19. A method for treating or preventing a condition associated with elevated ACTH, cortisol, aldosterone, and/or corticosterone in a subject, comprising administering to a subject in need thereof an effective amount of an anti-human adrenocorticotrophic hormone ("ACTH") antibody or antibody fragment according to any one of **claims 1-12** or composition according to **claim 13**, and optionally administering another therapeutic agent or therapeutic regimen, wherein optionally the condition is selected from the group consisting of: ACTH-driven hypercortisolism, acute coronary syndrome, acute heart failure, atherosclerosis, atrial fibrillation, cachexia, cancer, Cushing's Syndrome resulting from ectopic ACTH expression, Cushing's Syndrome resulting from ectopic ACTH expression associated with small cell lung cancer, Cushing's Syndrome resulting from ectopic ACTH expression associated with non-small cell lung cancer (NSCLC), Cushing's Syndrome resulting from ectopic

ACTH expression associated with pancreatic carcinoma, Cushing's Syndrome resulting from ectopic ACTH expression associated with neural tumors, Cushing's Syndrome resulting from ectopic ACTH expression associated with thymoma, cardiac conditions, cardiac fibrosis, cardiovascular disorders, chronic renal failure, chronic stress syndrome, cognitive dysfunction, Alzheimer's disease, congestive heart failure, Conn's syndrome, coronary heart diseases, Cushing's Disease, Cushing's Syndrome, depression, anxiety disorders, diabetes, endothelial dysfunction, exercise intolerance, familial hyperaldosteronism, fibrosis, galactorrhea, heart failure, hyperaldosteronism, hypercortisolemia, hypertension, hyperinsulinemia, hypokalemia, impaired cardiac function, increased formation of collagen, inflammation, metabolic syndrome, muscle atrophy, conditions associated with muscle atrophy, myocardiac fibrosis, nephropathy, obesity, post-myocardial infarction, primary hyperaldosteronism, remodeling following hypertension, renal failure, restenosis, secondary hyperaldosteronism, adrenal hyperplasia, congenital adrenal hyperplasia, sleep apnea, sleep disorders, stress related conditions, and syndrome X, wherein said subject is a human, or wherein said subject is a non-human animal, a dog, a cat, or a horse.

20. The method of **claim 19**, wherein said other therapeutic agent or regimen comprises: Accupril (quinapril), Aceon (perindopril), Adalat, Adalat CC, Aldactone (spironolactone), aldosterone receptor blockers, alpha-adrenergic receptor blockers, alpha-glucosidase inhibitors, Altace (ramipril), Alteplase, aminoglutethimide (Cytadren®), amiodarone, angiotensin converting enzyme (ACE) Inhibitors, angiotensin II receptor antagonists, Angiotensin II receptor blockers (ARBs), antiarrhythmics, anti-cholesterol drugs, anti-clotting agents, antidiabetogenic drugs, anti-hypertensive agents, antiplatelet drugs, ApoA-l mimics, aspirin, Atacand (candesartan), Avapro (irbesartan), beta blockers, beta-adrenergic receptor blockers, Betapace (sotalol), BiDil (hydralazine with isosorbide dinitrate), biguanides, blood thinners, Brevibloc (esmolol), Bumex (bumetanide), cabergoline (Dostinex®), Caduet (a combination of a statin cholesterol drug and amlodipine), Calan, Calan SR, Calcium channel blockers, Capoten (captopril), Cardene, Cardene SR (nicardipine), Cardizem, Cardizem CD, Cardizem SR, CETP inhibitors, conivaptan (Vaprisol®), Cordarone (amiodarone), Coreg (carvedilol), Covera-HS, Cozaar (losartan), cyproheptadine (Periactin® or Peritol®), Demadex (torsemide), digoxin, Dilacor XR, Dilatrate-SR, Diltia XT, Diovan (valsartan), dipeptidyl peptidase-4 inhibitors, diuretics, Dobutrex (dobutamine), drugs that suppress ACTH secretion, drugs that suppress cortisol secretion, dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, endothelin receptor blockers, Esidrix (hydrochlorothiazide), etomidate (Amidate®), Fragmin, gemfibrozil (Lopid, Gemcor), glucocorticoid receptor antagonists, heart failure drugs, Heparin, HMG-Co-A reductase inhibitors, cholestyramine (Questran), IMDUR (isosorbide mononitrate), Inderal (propranolol), inhibitors of a Na-K-ATPase membrane pump, inhibitors of steroidogenesis, insulin therapies, Iso-Bid, Isonate, Isoptin, Isoptin SR, Isordil (isosorbide dinitrate), Isotrate, ketoconazole (Nizoral®), Lasix (furosemide), lixivaptan (VPA-985), Lopressor, Lotensin

(benazepril), Lovenox, Mavik (trandolapril), meglitinides, metyrapone (Metopirone®), Micardis (telmisartan), mifepristone (Korlym®), mitotane (Lysodren®), Monopril (fosinopril), neutral endopeptidase (NEP) inhibitors, Normodyne, Norvasc (amlodipine), obesity-reducing agents, Omacor, pantethine, pasireotide (Signifor®), Plendil (felodipine), PPAR-gamma agonists, Primacor (milrinone), Prinivil, Procanbid (procainamide), Procardia, Procardia XL (nifedipine), renin inhibitors, Reteplase, rosiglitazone (Avandia®), satavaptan (SR121463, planned trade name Aquilda®), Sectral (acebutolol), somatostatin analogs, Sorbitrate (isosorbide dinitrate), statins, Streptokinase, Sular (nisoldipine), sulfonylurea, Tambocor (flecainide), Tenecteplase, Tenormin (atenolol), thiazolidinediones, Tiazac (diltiazem), Tissue plasminogen activator (tPA), tolvaptan (OPC-41061), Toprol-XL (metoprolol), Trandate (labetalol), Univasc (moexipril), Urokinase, valproic acid (Depakote®), vaptans, Vascor (bepridil), vasodilators, Vasodilators, vasopressin antagonists, Vasotec (enalapril), Verelan, Verelan PM (verapamil), warfarin (Coumadin), Zaroxolyn (metolazone), Zebeta (bisoprolol), or Zestril (lisinopril).

21. A pharmaceutical composition for therapeutic, prophylactic, or diagnostic use, comprising a therapeutically, prophylactically, or diagnostically effective amount of at least one anti-human ACTH antibody or antibody fragment according to any one of **claims 1-12** wherein optionally said composition: is suitable for subcutaneous administration, is suitable for intravenous administration, or is lyophilized; and optionally further comprises a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative, another active agent.

Figure 1A

Antibody Heavy chain Protein features

Sequence Name	FR1	CDR1	FR2	CDR2
Ab1	QSVKESGGRLVTPGTPLTLTCTVSG	FSLS	NYDMI WVRQAPGKGLESIG	MIYDDGDTYYASWAKG
Ab2	QSVEESGGRLVTPGTPLTLTCTVSG	FSLS	KYDMI WVRQAPGKGLESIG	IIYDDGDTYYASWAKG
Ab3	QSLEESGGRLVTPGTPLTLTCTVSG	SSLS	NFDMI WVRQAPGKGLESIG	IIYDFGSTYYASWAKG
Ab4	QSVEESGGRLVTPGTPLTLTYTVSG	FSLS	KHDMI WVRQAPGKGLESIG	IIYDDGDTYYANWAKG
Ab5	QSVEESGGRLVTPGTPLTLTCTVSG	FSLS	SYAMS WVRQAPGEGLEWIG	IISDSGSTYYASWAKG
Ab6	QSVEESGGRLVTPGTPLTLTCTVSG	FSLT	DYAMS WVRQAPGEGLEWIG	IISDSGSTYYASWAKG
Ab7	QSVEESGGRLVTPGTPLTLTCTVSG	FSLS	SYAMS WVRQAPGEGLEWIG	IISDSGSTYYASWAKG
Ab9	QSVEESGGRLVTPGTPLTLTCTVSG	FSLN	SYAMS WVRQAPGEGLEWIG	IISDSGRTYYASWAKG
Ab10	QSVEESGGRLVTPGTPLTLTCTVSG	FSLS	SADMI WVRQAPGKGLESIG	MIYDDGDTYYATWAKG
Ab11	QSLEESGGRLVTPGTSLTLTCTASG	FSLS	AYDIL WVRQAPGKGLESIG	MMYDDGDTYYATWAKG
Ab12	QSVEESGGRLVTPGTPLTLTCTVSG	SSLS	DYDMI WVRQAPGKGLESIG	IIYDDGDTYYATWAKG
Ab1.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFTVS	NYDMI WVRQAPGKGLESIG	MIYDDGDTYYASSAKG
Ab2.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFTVS	KYDMI WVRQAPGKGLESIG	IIYDDGDTYYASSAKG
Ab3.H	EVQLVESGGGLVQPGGSLRLSCAAS	GSSLS	NFDMI WVRQAPGKGLESIG	IIYDFGSTYYASSAKG
Ab4.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFTVS	KHDMI WVRQAPGKGLESIG	IIYDDGDTYYANSAKG
Ab6.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFSLT	DYAMS WVRQAPGKGLEWIG	IISDSGSTYYASSAKG
Ab7.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFSLS	SYAMS WVRQAPGKGLEWIG	IISDSGSTYYASSAKG
Ab7A.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFSLS	SYAMS WVRQAPGKGLEWIG	IISDSGSTYYASSAKG
Ab10.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFTVS	SADMI WVRQAPGKGLESIG	MIYDDGDTYYATSAKG
Ab11.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFTVS	AYDIL WVRQAPGKGLESIG	MMYDDGDTYYATSAKG
Ab11A.H	EVQLVESGGGLVQPGGSLRLSCAAS	GFTVS	AYDIL WVRQAPGKGLESIG	MMYDDGDTYYATSAKG
Ab12.H	EVQLVESGGGLVQPGGSLRLSCAAS	GSSLS	DYDMI WVRQAPGKGLESIG	IIYDDGDTYYATSAKG

Figure 1B

Antibody Heavy chain Protein features

Sequence Name	FR3	CDR3	FR4
Ab1	RFTISKTSTTVDLKIISPTTEDTATYFCVK	GVSNH	WGPGTLVTVSS
Ab2	RFTISQTSTTVDLKIISPTTEDTATYFCVK	GVSNI	WGQGTLVTVSS
Ab3	RFTISRTSSTTVDLKIISPTIEDTATYFCVK	GVSNI	WGQGTLVTVSS
Ab4	RFTISKTSTTVDLKIISPTTEDTATYFCVK	GVSNI	WGPGTLVTVSS
Ab5	RFTISKTSTTVDLKITSPTTEDTATYFCAR	EPEYGYDDYGDWVSDL	WGQGTLVTVSS
Ab6	RFTFSKTSTTVDLRITSPTTEDTATYFCAR	EPEYGYDEYGDWVSDL	WGPGTLVTVSS
Ab7	RFTISKTSTTVDLRITSPTTEDTATYFCAR	EPEYGYDDYGDWVSDL	WGQGTLVTVSS
Ab9	RFTISKTSTTVDLKITSPTTEDTATYFCAR	EPEYGYDDYGDWVSDL	WGPGTLVTVSS
Ab10	RFTISKTSTTVDLKIISPTTEDTATYFCVK	GVSSV	WGQGTLVTVSS
Ab11	RFIISRTSTTMDLKIISPTTEDTATYFCVK	GVSNI	WGQGTLVTVSS
Ab12	RFTISKTSTTVDLRIISPTTEDTATYFCVK	GVSNM	WGPGTLVTVSS
Ab1.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVK	GVSNH	WGQGTLVTVSS
Ab2.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVK	GVSNI	WGQGTLVTVSS
Ab3.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVK	GVSNI	WGQGTLVTVSS
Ab4.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVK	GVSNI	WGQGTLVTVSS
Ab6.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EPEYGYDEYGDWVSDL	WGQGTLVTVSS
Ab7.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EPEYGYDDYGDWVSDL	WGQGTLVTVSS
Ab7A.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EPEYGYDDYGDWVSDL	WGQGTLVTVSS
Ab10.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVK	GVSSV	WGQGTLVTVSS
Ab11.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVK	GVSNI	WGQGTLVTVSS
Ab11A.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVK	GVSNI	WGQGTLVTVSS
Ab12.H	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCVK	GVSNM	WGQGTLVTVSS

Figure 1C

Antibody Heavy chain Protein features

Sequence Name	Constant region
Ab1	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab2	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab3	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab4	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab5	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab6	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab7	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab9	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab10	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab11	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab12	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab1.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab2.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab3.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab4.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab6.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab7.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab7A.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab10.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab11.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab11A.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
Ab12.H	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL

Figure 1D

Antibody Heavy chain Protein features

Sequence Name	Constant region
Ab1	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab2	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab3	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab4	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab5	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab6	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab7	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab9	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab10	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab11	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab12	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab1.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab2.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab3.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab4.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab6.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab7.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab7A.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab10.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab11.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab11A.H	GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
Ab12.H	GTQTYICNVNHKPSNTKVDARVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH

Figure 1E

Antibody Heavy chain Protein features

Sequence Name	Constant region
Ab1	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab2	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab3	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab4	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab5	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab6	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab7	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab9	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab10	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab11	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab12	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab1.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab2.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab3.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab4.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab6.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab7.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab7A.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab10.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab11.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab11A.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
Ab12.H	EDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP

Figure 1F

Antibody Heavy chain Protein features

Sequence Name	Constant region
Ab1	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab2	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab3	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab4	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab5	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab6	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab7	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab9	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab10	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab11	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab12	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab1.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab2.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab3.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab4.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab6.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab7.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab7A.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab10.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab11.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab11A.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
Ab12.H	REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ

Figure 1G

Antibody Heavy chain Protein features

Sequence Name	Constant region	
Ab1	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:1)
Ab2	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:41)
Ab3	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:81)
Ab4	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:121)
Ab5	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:161)
Ab6	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:201)
Ab7	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:241)
Ab9	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:281)
Ab10	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:321)
Ab11	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:361)
Ab12	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:401)
Ab1.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:441)
Ab2.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:481)
Ab3.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:521)
Ab4.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:561)
Ab6.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:601)
Ab7.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:641)
Ab7A.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:681)
Ab10.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:721)
Ab11.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:761)
Ab11A.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:801)
Ab12.H	QGNVFSCSVMHEALHNHYTQKSLSLSPGK	(SEQ_ID_NO:841)

Figure 2A

Antibody Light chain Protein features

Sequence Name	FR1	CDR1	FR2	CDR2
Ab1	DVVMTQTPASVEAAVGGTVTIKC	QASQSISSYLA	WYQQKPGQPPKLLIY	SASTLAS
Ab2	DVVMTQTPASVEAAVGGTVTIKC	QASQSISNYLA	WYQQKTGQPPKLLIY	SASTLAS
Ab3	DVVMTQTPASVEAAVGGTVTIKC	QASEDISSNLA	WYQQKLGQPPKLLIY	SASTLAS
Ab4	DVVMTQTPASVEAAVGGTVTIKC	RASQSISVYLA	WYQQKAGQPPKLLIY	QASKLAS
Ab5	ADIVMTQTPASVSEPVGGTVTIKC	QASQSISSYLS	WYQQKPGQPPKLLIY	RASTLAS
Ab6	ADIVMTQTPASVEAAVGGAVTIKC	QATQSIGNNLA	WYQQKPGQPPKLLIY	RASTLAS
Ab7	ADIVMTQTPASVEAAVGGTVTIKC	QASQSISDYLS	WYQQKPGQPPKLLIY	RASTLAS
Ab9	ADVVMTQTPASVEAAVGGTVTIKC	QASQSISSYLS	WYQQKPGQPPKLLIY	RASTLAS
Ab10	DVVMTQTPASVEAAVGGTVTINC	QASENIYRSLA	WYQQKPGQPPKLLIY	SASTLAS
Ab11	DIVMTQIPASVEAAVGGTVTIKC	QASQSIDSSLA	WYQQKPGQPPKLLIY	SASTLAS
Ab12	DVVMTQTPSSVSAAVGGTVTIKC	QASQSIGSSLA	WYQQKPGQRPKLLIY	AASTLAS
Ab1.H	DIQMTQSPSTLSASVGDRVTITC	QASQSISSYLA	WYQQKPGKAPKLLIY	SASTLAS
Ab2.H	DIQMTQSPSTLSASVGDRVTITC	QASQSISNYLA	WYQQKPGKAPKLLIY	SASTLAS
Ab3.H	DIQMTQSPSTLSASVGDRVTITC	QASEDISSNLA	WYQQKPGKAPKLLIY	SASTLAS
Ab4.H	DIQMTQSPSTLSASVGDRVTITC	RASQSISVYLA	WYQQKPGKAPKLLIY	QASKLAS
Ab6.H	DIQMTQSPSTLSASVGDRVTITC	QATQSIGNNLA	WYQQKPGKAPKLLIY	RASTLAS
Ab7.H	DIQMTQSPSTLSASVGDRVTITC	QASQSISDYLS	WYQQKPGKAPKLLIY	RASTLAS
Ab7A.H	ADIQMTQSPSTLSASVGDRVTITC	QASQSISDYLS	WYQQKPGKAPKLLIY	RASTLAS
Ab10.H	DIQMTQSPSTLSASVGDRVTITC	QASENIYRSLA	WYQQKPGKAPKLLIY	SASTLAS
Ab11.H	DIQMTQSPSTLSASVGDRVTITC	QASQSIDSSLA	WYQQKPGKAPKLLIY	SASTLAS
Ab11A.H	DIQMTQSPSTLSASVGDRVTITC	QASQSIGSSLA	WYQQKPGKAPKLLIY	SASTLAS
Ab12.H	DIQMTQSPSTLSASVGDRVTITC	QASQSIGSSLA	WYQQKPGKAPKLLIY	AASTLAS

Figure 2B

Antibody Light chain Protein features

Sequence Name	FR3	CDR3	FR4
Ab1	GVPSRFKGRGSGTEFTLTISDLECADAATYYC	QSYDGSSGSSYGVG	FGGGTEVVVKR
Ab2	GVPSRFKGSGSGTEFTLTISDLECADAATYYC	QSYEGSSSSSYGVG	FGGGTEVVVKR
Ab3	GVPSRFKGSGSGTEFTLAISDLECADAATYYC	QSYDGSSSSSYGIG	FGGGTEVVVKR
Ab4	GVPSRFKGSGSGTEFTLTISDLECADAATYYC	QSYDGSSSSSYGVG	FGGGTEVVVKR
Ab5	GVPSRFKGSGSGTQFTLTISDLECADAATYYC	QSYYYSSSITYRNA	FGGGTEVVVKR
Ab6	GVPSRFKGSGSGTEFTLTISDLECADAATYYC	QSYYYSSSITYHNA	FGGGTEVVVKR
Ab7	GVPSRFKGSGSGTQFTLTISDLECADAATYYC	QSYYYSSSITYRNA	FGGGTEVVVKR
Ab9	GVPSRFKGSGSGTQFTLTISDLECADAATYYC	QSYYYSSSITYRNA	FGGGTEVVVKR
Ab10	GVPSRFKGSGSGTEFTLTISDLECADAATYYC	QSYDGSSSSSYGVG	FGGGTEVVVKR
Ab11	GVPSRFKGSGSGTEFTLTIGDLECADAATYYC	QSYDGSSSSYYGIG	FGGGTEVVVKR
Ab12	GVPSRFKGSGSGTEFTLTISDLECADAATYYC	QSYDGSSSSSYGVG	FGGGTEVVVKR
Ab1.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYDGSSGSSYGVG	FGGGTKVEIKR
Ab2.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYEGSSSSSYGVG	FGGGTKVEIKR
Ab3.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYDGSSSSSYGIG	FGGGTKVEIKR
Ab4.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYDGSSSSSYGVG	FGGGTKVEIKR
Ab6.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYYYSSSITYHNA	FGGGTKVEIKR
Ab7.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYYYSSSITYRNA	FGGGTKVEIKR
Ab7A.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYYYSSSITYRNA	FGGGTKVEIKR
Ab10.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYDGSSSSSYGVG	FGGGTKVEIKR
Ab11.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYDGSSSSYYGIG	FGGGTKVEIKR
Ab11A.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYEGSSSSYYGIG	FGGGTKVEIKR
Ab12.H	GVPSRFSGSGSGTEFTLTISSLQPDDFATYYC	QSYDGSSSSSYGVG	FGGGTKVEIKR

Figure 2C

Antibody Light chain Protein features

Sequence Name	Constant region
Ab1	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab2	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab3	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab4	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab5	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab6	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab7	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab9	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab10	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab11	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab12	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab1.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab2.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab3.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab4.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab6.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab7.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab7A.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab10.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab11.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab11A.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
Ab12.H	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA

Figure 2D

Antibody Light chain Protein features

Sequence Name	Constant region	
Ab1	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:21)
Ab2	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:61)
Ab3	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:101)
Ab4	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:141)
Ab5	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:181)
Ab6	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:221)
Ab7	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:261)
Ab9	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:301)
Ab10	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:341)
Ab11	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:381)
Ab12	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:421)
Ab1.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:461)
Ab2.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:501)
Ab3.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:541)
Ab4.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:581)
Ab6.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:621)
Ab7.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:661)
Ab7A.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:701)
Ab10.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:741)
Ab11.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:781)
Ab11A.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:821)
Ab12.H	DYEKHKVYACEVTHQGLSSPVTKSFNRGEC	(SEQ_ID_NO:861)

Figure 3A

Antibody Heavy chain DNA features

Sequence Name	FR1
Ab1	cagtcagtgaaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab2	cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab3	cagtcgctggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab4	cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctacacagtctctggat
Ab5	cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab6	cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab7	cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab9	cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab10	cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab11	cagtcgctggaggagtccgggggtcgcctggtcacgcctgggacatccctgacactcacctgcacagcctctggat
Ab12	cagtcggtggaggagtccgggggtcgcctggtcacgcctgggacacccctgacactcacctgcacagtctctggat
Ab1.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab2.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab3.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab4.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab6.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab7.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab7A.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab10.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab11.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab11A.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg
Ab12.H	gaggtgcagcttgtggagtctgggggaggcttggtccagcctgggggggtcctgagactctcctgtgcagcctctg

Figure 3B

Antibody Heavy chain DNA features

Sequence Name	FR1	CDR1	FR2
Ab1	tctccctcagt	aactatgacatgatc	tgggtccgccaggctccagggaaggggctggaatccatcggg
Ab2	tctccctcagt	aagtatgacatgatc	tgggtccgccaggctccagggaaggggctggaatccatcggg
Ab3	cctccctcagt	aattttgacatgatc	tgggtccgccaggctccagggaaggggctggaatccatcggg
Ab4	tctccctcagt	aagcatgacatgatc	tgggtccgccaggctccagggaaggggctggaatccatcggg
Ab5	tctccctcagt	agctatgcaatgagc	tgggtccgccaggctccaggggaggggctggaatggatcgga
Ab6	tctccctcact	gactatgcaatgagc	tgggtccgccaggctccaggggaggggctggaatggatcgga
Ab7	tctccctcagt	agctatgcaatgagc	tgggtccgccaggctccaggggaggggctggaatggatcgga
Ab9	tctccctcaat	agttatgcaatgagc	tgggtccgccaggctccaggggaggggctggaatggatcgga
Ab10	tctccctcagt	agcgctgacatgatc	tgggtccgccaggctccagggaaggggctggaatccatcggg
Ab11	tctccctgagt	gcctatgacatcctc	tgggtccgccaggctccagggaagggcctggaatccatcgga
Ab12	cctccctcagt	gattatgacatgatc	tgggtccgccaggctccagggaaggggctggaatccatcggg
Ab1.H	gattcaccgtcagt	aactatgacatgatc	tgggtccgtcaggctccagggaaggggctggagtccatcgga
Ab2.H	gattcaccgtcagt	aagtatgacatgatc	tgggtccgtcaggctccagggaaggggctggagtccatcgga
Ab3.H	gttcctccctcagt	aactttgacatgatc	tgggtccgtcaggctccagggaaggggctggagtccatcgga
Ab4.H	gattcaccgtcagt	aagcatgacatgatc	tgggtccgtcaggctccagggaaggggctggagtccatcgga
Ab6.H	gattctccctcact	gactatgcaatgagc	tgggtccgtcaggctccagggaaggggctggagtggatcgga
Ab7.H	gattctccctcagt	agctatgcaatgagc	tgggtccgtcaggctccagggaaggggctggagtggatcgga
Ab7A.H	gattctccctcagt	agctatgcaatgagc	tgggtccgtcaggctccagggaaggggctggagtggatcgga
Ab10.H	gattcaccgtcagt	agcgctgacatgatc	tgggtccgtcaggctccagggaaggggctggagtccatcgga
Ab11.H	gattcaccgtcagt	gcctatgacatcctc	tgggtccgtcaggctccagggaaggggctggagtccatcgga
Ab11A.H	gattcaccgtcagt	gcctatgacatcctc	tgggtccgtcaggctccagggaaggggctggagtccatcgga
Ab12.H	gatcctccctcagt	gattatgacatgatc	tgggtccgtcaggctccagggaaggggctggagtccatcgga

Figure 3C

Antibody Heavy chain DNA features

Sequence Name	CDR2	FR3
Ab1	atgatttatgatgatggtgacacat	actacgcgagttgggcgaaaggc	cgattcaccatctccaaaac	ctcgacca
Ab2	atcatttatgatgatggcgacacat	attacgcgagttgggcgaaaggc	cgattcaccatctcccaaac	ctcgacca
Ab3	atcatttatgattttggtagcacat	actacgcgagctgggcgaaaggc	cgcttcaccatctccagaac	ctcgtcga
Ab4	atcatttatgatgatggtgatacat	actacgcgaattgggcgaaaggc	cgattcaccatctccaaaac	ctcgacca
Ab5	atcattagtgatagtggtagcacat	actacgcgagctgggcgaaaggc	cgattcaccatctccaaaac	ctcgacca
Ab6	atcattagtgatagtggtagcacat	actacgcgagctgggcgaaaggc	cgattcaccttctccaaaac	ctcgacca
Ab7	atcattagtgatagtggtagcacat	actacgcgagctgggcgaaaggc	cgattcaccatctccaaaac	ctcgacca
Ab9	atcattagtgatagtggtaggacat	actacgcgagctgggcgaaaggc	cgattcaccatctccaaaac	ctcgacca
Ab10	atgatttatgatgatggtgacacat	actacgcgacttgggcgaaaggc	cgattcaccatctccaaaac	ctcgacca
Ab11	atgatgtatgatgatggtgacacat	actacgcgacttgggcgaaaggc	cgattcatcatctccagaac	ctcgacca
Ab12	atcatttatgatgatggtgacacat	actacgcgacttgggcgaaaggc	cgattcaccatctccaaaac	ctcgacca
Ab1.H	atgatttatgatgatggtgacacat	actacgctagttctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab2.H	atcatttatgatgatggcgacacat	attacgctagttctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab3.H	atcatttatgattttggtagcacat	actacgccagctctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab4.H	atcatttatgatgatggtgatacat	actacgctaattctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab6.H	atcattagtgatagtggtagcacat	actacgctagctctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab7.H	atcattagtgatagtggtagcacat	actacgcgagctctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab7A.H	atcattagtgatagtggtagcacat	actacgcgagctctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab10.H	atgatttatgatgatggtgacacat	actacgctacttctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab11.H	atgatgtatgatgatggtgacacat	actacgctacttctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab11A.H	atgatgtatgatgatggtgacacat	actacgctacttctgctaaaggc	cgattcaccatctccagaga	caattcca
Ab12.H	atcatttatgatgatggtgacacat	actacgctacttctgctaaaggc	cgattcaccatctccagaga	caattcca

Figure 3D

Antibody Heavy chain DNA features

Sequence Name	FR3
Ab1	cggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaa
Ab2	cggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaa
Ab3	ccacggtggatctgaaaatcatcagtccgacaattgaggacacggccacctatttctgtgtcaaa
Ab4	cggtggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaa
Ab5	cggtggatctgaaaatcaccagtccgacaaccgaggacacggccacctatttctgtgccaga
Ab6	cggtggatctgagaatccaccagtccgaccaccgaggacacggccacctatttctgtgccaga
Ab7	cggtggatctgagaatcaccagtccgacaaccgaggacacggccacctatttctgtgccaga
Ab9	cggtggatctgaaaatcaccagtccgacaaccgaggacacggccacctatttctgtgccaga
Ab10	cggtggatctgaagatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaa
Ab11	cgatggatctgaaaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaa
Ab12	cggtggatctgagaatcatcagtccgacaaccgaggacacggccacctatttctgtgtcaaa
Ab1.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
Ab2.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
Ab3.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
Ab4.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
Ab6.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctaga
Ab7.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctaga
Ab7A.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgctaga
Ab10.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
Ab11.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
Ab11A.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa
Ab12.H	agaacaccctgtatcttcaaatgaacagcctgagagctgaggacactgctgtgtattactgtgtcaaa

Figure 3E

Antibody Heavy chain DNA features

Sequence Name	CDR3	FR4
Ab1	ggtgtgagtaatcac	tggggcccaggcaccctcgtcaccgtct
Ab2	ggtgtgagtaatatc	tggggccaaggcaccctcgtcaccgtct
Ab3	ggtgtgagtaatatc	tggggccaaggcaccctcgtcaccgtct
Ab4	ggtgtgagtaatatc	tggggcccaggcaccctcgtcaccgtct
Ab5	gagcccgagtacggctacgatgactatggtgattgggtttctgactta	tggggccagggcaccctggtcaccgtct
Ab6	gagcccgagtacggctacgatgagtatggtgattgggtttctgactta	tggggcccaggcaccctcgtcaccgtct
Ab7	gagcccgagtacggctacgatgactatggtgattgggtttctgactta	tggggccaaggcaccctcgtcaccgtct
Ab9	gagcccgagtacggctacgatgactatggtgattgggtttctgactta	tggggcccaggcaccctcgtcaccgtct
Ab10	ggtgtgagtagtgtc	tggggccaggggaccctggtcaccgtct
Ab11	ggtgtgagtaatatc	tggggccaaggcaccctggtcaccgtct
Ab12	ggtgtgagtaatatg	tggggcccggggaccctggtcaccgtct
Ab1.H	ggtgtgagtaatcac	tggggccaagggaccctcgtcaccgtct
Ab2.H	ggtgtgagtaatatc	tggggccaagggaccctcgtcaccgtct
Ab3.H	ggtgtgagtaatatc	tggggccaagggaccctcgtcaccgtct
Ab4.H	ggtgtgagtaatatc	tggggccaagggaccctcgtcaccgtct
Ab6.H	gagcccgagtacggctacgatgagtatggtgattgggtttctgactta	tggggccaagggaccctcgtcaccgtct
Ab7.H	gagcccgagtacggctacgatgactatggtgattgggtttctgactta	tggggccaagggaccctcgtcaccgtct
Ab7A.H	gagcccgagtacggctacgatgactatggtgattgggtttctgactta	tggggccaagggaccctcgtcaccgtct
Ab10.H	ggtgtgagtagtgtc	tggggccaagggaccctcgtcaccgtct
Ab11.H	ggtgtgagtaatatc	tggggccaagggaccctcgtcaccgtct
Ab11A.H	ggtgtgagtaatatc	tggggccaagggaccctcgtcaccgtct
Ab12.H	ggtgtgagtaatatg	tggggccaagggaccctcgtcaccgtct

Figure 3F

Antibody Heavy chain DNA features

Sequence Name	FR4	Constant region
Ab1	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab2	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab3	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab4	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab5	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab6	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab7	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab9	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab10	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab11	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab12	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab1.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab2.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab3.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab4.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab6.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab7.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab7A.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab10.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab11.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab11A.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg
Ab12.H	cgagc	gcctccaccaagggcccatcggtcttccccctggcaccctcctccaagagcacctctgggggcacagcgg

Figure 3G

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab2	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab3	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab4	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab5	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab6	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab7	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab9	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab10	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab11	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab12	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab1.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab2.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab3.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab4.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab6.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab7.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab7A.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab10.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab11.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab11A.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg
Ab12.H	ccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcg

Figure 3H

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab2	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab3	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab4	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab5	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab6	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab7	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab9	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab10	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab11	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab12	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab1.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab2.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab3.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab4.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab6.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab7.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab7A.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab10.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab11.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab11A.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca
Ab12.H	gcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctcca

Figure 3I

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab2	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab3	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab4	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab5	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab6	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab7	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab9	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab10	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab11	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab12	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab1.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab2.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab3.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab4.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab6.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab7.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab7A.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab10.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab11.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg
Ab11A.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagaaagttg
Ab12.H	gcagcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacgcgagagttg

Figure 3J

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab2	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab3	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab4	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab5	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab6	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab7	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab9	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab10	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab11	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab12	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab1.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab2.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab3.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab4.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab6.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab7.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab7A.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab10.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab11.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab11A.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct
Ab12.H	agcccaaatcttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtct

Figure 3K

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab2	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab3	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab4	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab5	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab6	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab7	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab9	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab10	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab11	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab12	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab1.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab2.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab3.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab4.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab6.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab7.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab7A.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab10.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab11.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab11A.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg
Ab12.H	tcctcttcccccaaaacccaaggacaccctcatgatctcccggaccccctgaggtcacatgcgtggtggtggacg

Figure 3L

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagc
Ab2	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagc
Ab3	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagc
Ab4	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagc
Ab5	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab6	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagc
Ab7	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagc
Ab9	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab10	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab11	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab12	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab1.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab2.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab3.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab4.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab6.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab7.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab7A.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab10.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab11.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab11A.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc
Ab12.H	tgagccacgaagaccctgaggtcaagttcaactggtacgtggacggcgtgaggtgcataatgccaagacaaagc

Figure 3M

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab2	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab3	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab4	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab5	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab6	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab7	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab9	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab10	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab11	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab12	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab1.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab2.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab3.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab4.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab6.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab7.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab7A.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab10.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab11.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab11A.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg
Ab12.H	cgcgggaggagcagtacgccagcacgtaccgtgtggtcagcgtcctcaccgtcctgcaccaggactggctgaatg

Figure 3N

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab2	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab3	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab4	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab5	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab6	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab7	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab9	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab10	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab11	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab12	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab1.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab2.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab3.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab4.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab6.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab7.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab7A.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab10.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab11.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab11A.H	gcaaggagtacaagtgcaaggtctccaacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag
Ab12.H	gcaaggagtacaagtgcaaggtctc caacaaagccctcccagccccatc gagaaaaccatctccaaagccaaag

Figure 30

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab2	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab3	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab4	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab5	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab6	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab7	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab9	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab10	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab11	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab12	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab1.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab2.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab3.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab4.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab6.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab7.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab7A.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab10.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab11.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab11A.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga
Ab12.H	ggcagccccgagaaccacaggtgtacaccctgcccccatcccgggaggagatgaccaagaaccaggtcagcctga

Figure 3P

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab2	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab3	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab4	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab5	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab6	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab7	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab9	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab10	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab11	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab12	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab1.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab2.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab3.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab4.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab6.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab7.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab7A.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab10.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab11.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab11A.H	cctgcctggtcaaaggcttctatccc agcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact
Ab12.H	cctgcctggtcaaaggcttctatcc cagcgacatcgccgtggagtgggag agcaatgggcagccggagaacaact

Figure 3Q
Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab2	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab3	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab4	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab5	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab6	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab7	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab9	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab10	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab11	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab12	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab1.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab2.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab3.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab4.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab6.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab7.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab7A.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab10.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab11.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab11A.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca
Ab12.H	acaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaagctcaccgtggacaagagca

Figure 3R
Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab2	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab3	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab4	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab5	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab6	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab7	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab9	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab10	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab11	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab12	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab1.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab2.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab3.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab4.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab6.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab7.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab7A.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab10.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab11.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab11A.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc
Ab12.H	ggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcc

Figure 3S

Antibody Heavy chain DNA features

Sequence Name	Constant region
Ab1	tctccctgtctccgggtaaa (SEQ_ID_NO:11)
Ab2	tctccctgtctccgggtaaa (SEQ_ID_NO:51)
Ab3	tctccctgtctccgggtaaa (SEQ_ID_NO:91)
Ab4	tctccctgtctccgggtaaa (SEQ_ID_NO:131)
Ab5	tctccctgtctccgggtaaa (SEQ_ID_NO:171)
Ab6	tctccctgtctccgggtaaa (SEQ_ID_NO:211)
Ab7	tctccctgtctccgggtaaa (SEQ_ID_NO:251)
Ab9	tctccctgtctccgggtaaa (SEQ_ID_NO:291)
Ab10	tctccctgtctccgggtaaa (SEQ_ID_NO:331)
Ab11	tctccctgtctccgggtaaa (SEQ_ID_NO:371)
Ab12	tctccctgtctccgggtaaa (SEQ_ID_NO:411)
Ab1.H	tctccctgtctccgggtaaa (SEQ_ID_NO:451)
Ab2.H	tctccctgtctccgggtaaa (SEQ_ID_NO:491)
Ab3.H	tctccctgtctccgggtaaa (SEQ_ID_NO:531)
Ab4.H	tctccctgtctccgggtaaa (SEQ_ID_NO:571)
Ab6.H	tctccctgtctccgggtaaa (SEQ_ID_NO:611)
Ab7.H	tctccctgtctccgggtaaa (SEQ_ID_NO:651)
Ab7A.H	tctccctgtctccgggtaaa (SEQ_ID_NO:691)
Ab10.H	tctccctgtctccgggtaaa (SEQ_ID_NO:731)
Ab11.H	tctccctgtctccgggtaaa (SEQ_ID_NO:771)
Ab11A.H	tctccctgtctccgggtaaa (SEQ_ID_NO:811)
Ab12.H	tctccctgtctccgggtaaa (SEQ_ID_NO:851)

Figure 4A
Antibody Light chain DNA features

Sequence Name	FR1
Ab1	gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgc
Ab2	gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgc
Ab3	gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgc
Ab4	gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgc
Ab5	gctgacattgtgatgacccagactccagcctccgtgtctgaacctgtgggaggcacagtcaccatcaagtgc
Ab6	gctgacattgtgatgacccagactccagcctccgtggaggcagctgtgggaggcgcagtcaccatcaagtgc
Ab7	gctgacattgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgc
Ab9	gctgacgttgtgatgacccagactccagcctccgtggaggctgctgtgggaggcacagtcaccatcaagtgc
Ab10	gatgttgtgatgacccagactccagcctccgtggaggcagctgtgggaggcacagtcaccatcaattgc
Ab11	gacattgtgatgacccagattccagcctccgtggaggcagctgtgggaggcacagtcaccatcaagtgc
Ab12	gacgtcgtgatgacccagactccatcctccgtgtctgcagctgtgggaggcacagtcaccatcaagtgc
Ab1.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab2.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab3.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab4.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab6.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab7.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab7A.H	gctgacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab10.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab11.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab11A.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt
Ab12.H	gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgt

Figure 4B

Antibody Light chain DNA features

Sequence Name	CDR1	FR2
Ab1	caggccagtcagagcattagtagtt acttagcc	tggtatcagcagaaaccagggcagc ctcccaaactcctgatct
Ab2	caggccagtcagagcattagtaact acttagcc	tggtatcagcagaaaacagggcagc ctcccaagctcctgatct
Ab3	caggccagtgaggatattagtagta atttagcc	tggtatcagcagaaattagggcagc ctcccaagctcctgatct
Ab4	cgggccagtcagagcattagtgtct acctcgcc	tggtatcagcagaaagcagggcagc ctcccaagctcctgatct
Ab5	caggccagtcagagcattagtagtt acttatcc	tggtatcagcagaaaccagggcagc ctcccaagctcctgatct
Ab6	caggccactcagagcattggtaata atttagcc	tggtatcagcagaaaccagggcagc ctcccaagctcctgatct
Ab7	caggccagtcagagcattagtgatt acttatcc	tggtatcagcagaaaccagggcagc ctcccaagctcctgatct
Ab9	caggccagtcagagcattagtagtt acttatcc	tggtatcagcagaaaccagggcagc ctcccaagctcctgatct
Ab10	caggccagtgagaacatttacaggt ctttagcc	tggtatcagcagaaaccagggcagc ctcccaagctcctgatct
Ab11	caggccagtcagagcattgatagta gcttggcc	tggtatcagcagaaaccagggcagc ctcccaagctcctgatct
Ab12	caggccagtcagagcattggtagta gcttagcc	tggtatcagcagaaaccagggcagc gtcccaagctcctgatct
Ab1.H	caggccagtcagagcattagtagtt acttagcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab2.H	caggccagtcagagcattagtaact acttagcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab3.H	caggccagtgaggatattagtagta acttagcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab4.H	agagccagtcagagcattagtgtct acctcgcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab6.H	caggccactcagagcattggtaata acttagcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab7.H	caggccagtcagagcattagtgatt acttatcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab7A.H	caggccagtcagagcattagtgatt acttatcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab10.H	caggccagtgagaacatttacaggt ctttagcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab11.H	caggccagtcagagcattgatagta gcttggcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab11A.H	caggccagtcagagcattggtagtagcttggcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct
Ab12.H	caggccagtcagagcattggtagta gcttagcc	tggtatcagcagaaaccaggaaaag cccctaagctcctgatct

Figure 4C

Antibody Light chain DNA features

Sequence Name	FR2	CDR2	FR3
Ab1	ac	tctgcatccactctggcatct	ggggtcccatcgcggttcaaaggcaggggatctgggacagaattcactctca
Ab2	ac	tctgcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtggatctgggacagagttcactctca
Ab3	ac	tctgcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtggatctgggacagagttcactctcg
Ab4	ac	caggcatccaaactggcctct	ggggtcccatcgcggttcaaaggcagtggatctgggacagagttcactctca
Ab5	ac	agggcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtggatctgggacacagttcactctca
Ab6	ac	agggcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtgggtctgggacagagttcactctca
Ab7	ac	agggcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtggatctgggacacagttcactctca
Ab9	at	agggcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtggatctgggacacagttcactctca
Ab10	ac	tctgcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtggatctgggacagagttcactctca
Ab11	at	tctgcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtggatctgggacagagttcactctca
Ab12	at	gctgcatccactctggcatct	ggggtcccatcgcggttcaaaggcagtggatctgggacagagttcactctca
Ab1.H	at	tctgcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab2.H	at	tctgcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab3.H	at	tctgcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaatttactctca
Ab4.H	at	caggcatccaaactggcctct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab6.H	at	agggcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab7.H	at	agggcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab7A.H	at	agggcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab10.H	at	tctgcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab11.H	at	tctgcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab11A.H	at	tctgcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca
Ab12.H	at	gctgcatccactctggcatct	ggagtcccatcaaggttcagcggcagtggatctggaacagaattcactctca

Figure 4D

Antibody Light chain DNA features

Sequence Name	FR3	CDR3
Ab1	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctatgatggtagtagtggtagtagtt
Ab2	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctatgagggtagtagtagtagtagtt
Ab3	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctatgatggtagtagtagtagtagtt
Ab4	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctatgatggtagtagtagtagtagtt
Ab5	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctattattatagtagtagtattactt
Ab6	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctattattatagtagtagtattactt
Ab7	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctattattatagtagtagtattactt
Ab9	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctattattatagtagtagtattactt
Ab10	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctatgatggtagtagtagtagtagtt
Ab11	ccatcggcgacctggagtgtgccgatgctgccacttactactgt	caaagctatgatggtagtagtagtagttatt
Ab12	ccatcagcgacctggagtgtgccgatgctgccacttactactgt	caaagctatgatggtagtagtagtagtagtt
Ab1.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctatgatggtagtagtggtagtagtt
Ab2.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctatgagggtagtagtagtagtagtt
Ab3.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctatgatggtagtagtagtagtagtt
Ab4.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctatgatggtagtagtagtagtagtt
Ab6.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctattactatagtagtagtattactt
Ab7.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctattactatagtagtagtattactt
Ab7A.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctattactatagtagtagtattactt
Ab10.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctatgatggtagtagtagtagtagtt
Ab11.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctatgatggtagtagtagtagttact
Ab11A.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctatgaaggtagtagtagtagttact
Ab12.H	ccatcagcagcctgcagcctgatgattttgcaacttactactgt	caaagctatgatggtagtagtagtagtagtt

Figure 4E

Antibody Light chain DNA features

Sequence Name	CDR3	FR4	Constant region
Ab1	atggtgttggt	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab2	atggtgttggt	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab3	atggtattggt	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab4	atggtgttggt	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab5	atcgtaatgct	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab6	atcataatgct	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab7	atcgtaatgct	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab9	atcgtaatgct	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab10	atggtgttggt	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab11	atggtattggt	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab12	atggtgttggt	ttcggcggagggaccgaggtggtggtcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab1.H	atggtgttggt	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtggctgcaccatctgtcttcatcttcc
Ab2.H	atggtgttggt	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtggctgcaccatctgtcttcatcttcc
Ab3.H	atggtattggt	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtggctgcaccatctgtcttcatcttcc
Ab4.H	atggtgttggt	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtggctgcaccatctgtcttcatcttcc
Ab6.H	atcataatgct	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab7.H	atcgtaatgct	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab7A.H	atcgtaatgct	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtagcggccccatctgtcttcatcttcc
Ab10.H	atggtgttggt	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtggctgcaccatctgtcttcatcttcc
Ab11.H	atggtattggt	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtggctgcaccatctgtcttcatcttcc
Ab11A.H	atggtattggt	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtggctgcaccatctgtcttcatcttcc
Ab12.H	atggtgttggt	ttcggcggaggaaccaaggtggaaatcaaacgt	acggtggctgcaccatctgtcttcatcttcc

Figure 4F

Antibody Light chain DNA features

Sequence Name	Constant region
Ab1	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab2	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab3	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab4	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab5	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab6	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab7	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab9	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab10	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab11	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab12	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab1.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab2.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab3.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab4.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab6.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab7.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab7A.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab10.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab11.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab11A.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg
Ab12.H	cgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagagg

Figure 4G

Antibody Light chain DNA features

Sequence Name	Constant region
Ab1	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab2	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab3	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab4	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab5	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab6	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab7	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab9	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab10	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab11	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab12	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab1.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab2.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab3.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab4.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab6.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab7.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab7A.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab10.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab11.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab11A.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca
Ab12.H	ccaaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagca

Figure 4H

Antibody Light chain DNA features

Sequence Name	Constant region
Ab1	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab2	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab3	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab4	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab5	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab6	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab7	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab9	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab10	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab11	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab12	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab1.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab2.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab3.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab4.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab6.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab7.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab7A.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab10.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab11.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab11A.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct
Ab12.H	aggacagcacctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcct

Figure 4I

Antibody Light chain DNA features

Sequence Name	Constant region	
Ab1	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:31)
Ab2	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:71)
Ab3	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:111)
Ab4	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:151)
Ab5	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:191)
Ab6	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:231)
Ab7	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:271)
Ab9	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:311)
Ab10	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:351)
Ab11	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:391)
Ab12	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:431)
Ab1.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:471)
Ab2.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:511)
Ab3.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:551)
Ab4.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:591)
Ab6.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:631)
Ab7.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:671)
Ab7A.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:711)
Ab10.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:751)
Ab11.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:791)
Ab11A.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:831)
Ab12.H	gcgaagtcacccatcagggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgt	(SEQ_ID_NO:871)

Figure 5

Antibody Heavy chain Protein features

Sequence Name	Variable region coordinates	SEQ ID NO:	CDR1 coordinates	SEQ ID NO:	CDR2 coordinates	SEQ ID NO:	CDR3 coordinates	SEQ ID NO:
Ab1	1-110	2	30-34	4	49-64	6	95-99	8
Ab2	1-110	42	30-34	44	49-64	46	95-99	48
Ab3	1-111	82	30-34	84	49-64	86	96-100	88
Ab4	1-110	122	30-34	124	49-64	126	95-99	128
Ab5	1-121	162	30-34	164	49-64	166	95-110	168
Ab6	1-121	202	30-34	204	49-64	206	95-110	208
Ab7	1-121	242	30-34	244	49-64	246	95-110	248
Ab9	1-121	282	30-34	284	49-64	286	95-110	288
Ab10	1-110	322	30-34	324	49-64	326	95-99	328
Ab11	1-110	362	30-34	364	49-64	366	95-99	368
Ab12	1-110	402	30-34	404	49-64	406	95-99	408
Ab1.H	1-113	442	31-35	444	50-65	446	98-102	448
Ab2.H	1-113	482	31-35	484	50-65	486	98-102	488
Ab3.H	1-113	522	31-35	524	50-65	526	98-102	528
Ab4.H	1-113	562	31-35	564	50-65	566	98-102	568
Ab6.H	1-124	602	31-35	604	50-65	606	98-113	608
Ab7.H	1-124	642	31-35	644	50-65	646	98-113	648
Ab7A.H	1-124	682	31-35	684	50-65	686	98-113	688
Ab10.H	1-113	722	31-35	724	50-65	726	98-102	728
Ab11.H	1-113	762	31-35	764	50-65	766	98-102	768
Ab11A.H	1-113	802	31-35	804	50-65	806	98-102	808
Ab12.H	1-113	842	31-35	844	50-65	846	98-102	848

Figure 6

Antibody Heavy chain Protein features

Sequence Name	FR1 coordinates	SEQ ID NO:	FR2 coordinates	SEQ ID NO:	FR3 coordinates	SEQ ID NO:	FR4 coordinates	SEQ ID NO:	Constant region coordinates	SEQ ID NO:
Ab1	1-29	3	35-48	5	65-94	7	100-110	9	111-440	10
Ab2	1-29	43	35-48	45	65-94	47	100-110	49	111-440	50
Ab3	1-29	83	35-48	85	65-95	87	101-111	89	112-441	90
Ab4	1-29	123	35-48	125	65-94	127	100-110	129	111-440	130
Ab5	1-29	163	35-48	165	65-94	167	111-121	169	122-451	170
Ab6	1-29	203	35-48	205	65-94	207	111-121	209	122-451	210
Ab7	1-29	243	35-48	245	65-94	247	111-121	249	122-451	250
Ab9	1-29	283	35-48	285	65-94	287	111-121	289	122-451	290
Ab10	1-29	323	35-48	325	65-94	327	100-110	329	111-440	330
Ab11	1-29	363	35-48	365	65-94	367	100-110	369	111-440	370
Ab12	1-29	403	35-48	405	65-94	407	100-110	409	111-440	410
Ab1.H	1-30	443	36-49	445	66-97	447	103-113	449	114-443	450
Ab2.H	1-30	483	36-49	485	66-97	487	103-113	489	114-443	490
Ab3.H	1-30	523	36-49	525	66-97	527	103-113	529	114-443	530
Ab4.H	1-30	563	36-49	565	66-97	567	103-113	569	114-443	570
Ab6.H	1-30	603	36-49	605	66-97	607	114-124	609	125-454	610
Ab7.H	1-30	643	36-49	645	66-97	647	114-124	649	125-454	650
Ab7A.H	1-30	683	36-49	685	66-97	687	114-124	689	125-454	690
Ab10.H	1-30	723	36-49	725	66-97	727	103-113	729	114-443	730
Ab11.H	1-30	763	36-49	765	66-97	767	103-113	769	114-443	770
Ab11A.H	1-30	803	36-49	805	66-97	807	103-113	809	114-443	810
Ab12.H	1-30	843	36-49	845	66-97	847	103-113	849	114-443	850

Figure 7

Antibody Light chain Protein features

Sequence Name	Variable region coordinates	SEQ ID NO:	CDR1 coordinates	SEQ ID NO:	CDR2 coordinates	SEQ ID NO:	CDR3 coordinates	SEQ ID NO:
Ab1	1-113	22	24-34	24	50-56	26	89-102	28
Ab2	1-113	62	24-34	64	50-56	66	89-102	68
Ab3	1-113	102	24-34	104	50-56	106	89-102	108
Ab4	1-113	142	24-34	144	50-56	146	89-102	148
Ab5	1-114	182	25-35	184	51-57	186	90-103	188
Ab6	1-114	222	25-35	224	51-57	226	90-103	228
Ab7	1-114	262	25-35	264	51-57	266	90-103	268
Ab9	1-114	302	25-35	304	51-57	306	90-103	308
Ab10	1-113	342	24-34	344	50-56	346	89-102	348
Ab11	1-113	382	24-34	384	50-56	386	89-102	388
Ab12	1-113	422	24-34	424	50-56	426	89-102	428
Ab1.H	1-113	462	24-34	464	50-56	466	89-102	468
Ab2.H	1-113	502	24-34	504	50-56	506	89-102	508
Ab3.H	1-113	542	24-34	544	50-56	546	89-102	548
Ab4.H	1-113	582	24-34	584	50-56	586	89-102	588
Ab6.H	1-113	622	24-34	624	50-56	626	89-102	628
Ab7.H	1-113	662	24-34	664	50-56	666	89-102	668
Ab7A.H	1-114	702	25-35	704	51-57	706	90-103	708
Ab10.H	1-113	742	24-34	744	50-56	746	89-102	748
Ab11.H	1-113	782	24-34	784	50-56	786	89-102	788
Ab11A.H	1-113	822	24-34	824	50-56	826	89-102	828
Ab12.H	1-113	862	24-34	864	50-56	866	89-102	868

Figure 8

Antibody Light chain Protein features

Sequence Name	FR1 coordinates	SEQ ID NO:	FR2 coordinates	SEQ ID NO:	FR3 coordinates	SEQ ID NO:	FR4 coordinates	SEQ ID NO:	Constant region coordinates	SEQ ID NO:
Ab1	1-23	23	35-49	25	57-88	27	103-113	29	114-219	30
Ab2	1-23	63	35-49	65	57-88	67	103-113	69	114-219	70
Ab3	1-23	103	35-49	105	57-88	107	103-113	109	114-219	110
Ab4	1-23	143	35-49	145	57-88	147	103-113	149	114-219	150
Ab5	1-24	183	36-50	185	58-89	187	104-114	189	115-220	190
Ab6	1-24	223	36-50	225	58-89	227	104-114	229	115-220	230
Ab7	1-24	263	36-50	265	58-89	267	104-114	269	115-220	270
Ab9	1-24	303	36-50	305	58-89	307	104-114	309	115-220	310
Ab10	1-23	343	35-49	345	57-88	347	103-113	349	114-219	350
Ab11	1-23	383	35-49	385	57-88	387	103-113	389	114-219	390
Ab12	1-23	423	35-49	425	57-88	427	103-113	429	114-219	430
Ab1.H	1-23	463	35-49	465	57-88	467	103-113	469	114-219	470
Ab2.H	1-23	503	35-49	505	57-88	507	103-113	509	114-219	510
Ab3.H	1-23	543	35-49	545	57-88	547	103-113	549	114-219	550
Ab4.H	1-23	583	35-49	585	57-88	587	103-113	589	114-219	590
Ab6.H	1-23	623	35-49	625	57-88	627	103-113	629	114-219	630
Ab7.H	1-23	663	35-49	665	57-88	667	103-113	669	114-219	670
Ab7A.H	1-24	703	36-50	705	58-89	707	104-114	709	115-220	710
Ab10.H	1-23	743	35-49	745	57-88	747	103-113	749	114-219	750
Ab11.H	1-23	783	35-49	785	57-88	787	103-113	789	114-219	790
Ab11A.H	1-23	823	35-49	825	57-88	827	103-113	829	114-219	830
Ab12.H	1-23	863	35-49	865	57-88	867	103-113	869	114-219	870

Figure 9

Antibody Heavy chain DNA features

Sequence Name	Variable region coordinates	SEQ ID NO:	CDR1 coordinates	SEQ ID NO:	CDR2 coordinates	SEQ ID NO:	CDR3 coordinates	SEQ ID NO:
Ab1	1-330	12	88-102	14	145-192	16	283-297	18
Ab2	1-330	52	88-102	54	145-192	56	283-297	58
Ab3	1-333	92	88-102	94	145-192	96	286-300	98
Ab4	1-330	132	88-102	134	145-192	136	283-297	138
Ab5	1-363	172	88-102	174	145-192	176	283-330	178
Ab6	1-363	212	88-102	214	145-192	216	283-330	218
Ab7	1-363	252	88-102	254	145-192	256	283-330	258
Ab9	1-363	292	88-102	294	145-192	296	283-330	298
Ab10	1-330	332	88-102	334	145-192	336	283-297	338
Ab11	1-330	372	88-102	374	145-192	376	283-297	378
Ab12	1-330	412	88-102	414	145-192	416	283-297	418
Ab1.H	1-339	452	91-105	454	148-195	456	292-306	458
Ab2.H	1-339	492	91-105	494	148-195	496	292-306	498
Ab3.H	1-339	532	91-105	534	148-195	536	292-306	538
Ab4.H	1-339	572	91-105	574	148-195	576	292-306	578
Ab6.H	1-372	612	91-105	614	148-195	616	292-339	618
Ab7.H	1-372	652	91-105	654	148-195	656	292-339	658
Ab7A.H	1-372	692	91-105	694	148-195	696	292-339	698
Ab10.H	1-339	732	91-105	734	148-195	736	292-306	738
Ab11.H	1-339	772	91-105	774	148-195	776	292-306	778
Ab11A.H	1-339	812	91-105	814	148-195	816	292-306	818
Ab12.H	1-339	852	91-105	854	148-195	856	292-306	858

Figure 10

Antibody Heavy chain DNA features

Sequence Name	FR1 coordinates	SEQ ID NO:	FR2 coordinates	SEQ ID NO:	FR3 coordinates	SEQ ID NO:	FR4 coordinates	SEQ ID NO:	Constant region coordinates	SEQ ID NO:
Ab1	1-87	13	103-144	15	193-282	17	298-330	19	331-1320	20
Ab2	1-87	53	103-144	55	193-282	57	298-330	59	331-1320	60
Ab3	1-87	93	103-144	95	193-285	97	301-333	99	334-1323	100
Ab4	1-87	133	103-144	135	193-282	137	298-330	139	331-1320	140
Ab5	1-87	173	103-144	175	193-282	177	331-363	179	364-1353	180
Ab6	1-87	213	103-144	215	193-282	217	331-363	219	364-1353	220
Ab7	1-87	253	103-144	255	193-282	257	331-363	259	364-1353	260
Ab9	1-87	293	103-144	295	193-282	297	331-363	299	364-1353	300
Ab10	1-87	333	103-144	335	193-282	337	298-330	339	331-1320	340
Ab11	1-87	373	103-144	375	193-282	377	298-330	379	331-1320	380
Ab12	1-87	413	103-144	415	193-282	417	298-330	419	331-1320	420
Ab1.H	1-90	453	106-147	455	196-291	457	307-339	459	340-1329	460
Ab2.H	1-90	493	106-147	495	196-291	497	307-339	499	340-1329	500
Ab3.H	1-90	533	106-147	535	196-291	537	307-339	539	340-1329	540
Ab4.H	1-90	573	106-147	575	196-291	577	307-339	579	340-1329	580
Ab6.H	1-90	613	106-147	615	196-291	617	340-372	619	373-1362	620
Ab7.H	1-90	653	106-147	655	196-291	657	340-372	659	373-1362	660
Ab7A.H	1-90	693	106-147	695	196-291	697	340-372	699	373-1362	700
Ab10.H	1-90	733	106-147	735	196-291	737	307-339	739	340-1329	740
Ab11.H	1-90	773	106-147	775	196-291	777	307-339	779	340-1329	780
Ab11A.H	1-90	813	106-147	815	196-291	817	307-339	819	340-1329	820
Ab12.H	1-90	853	106-147	855	196-291	857	307-339	859	340-1329	860

Figure 11

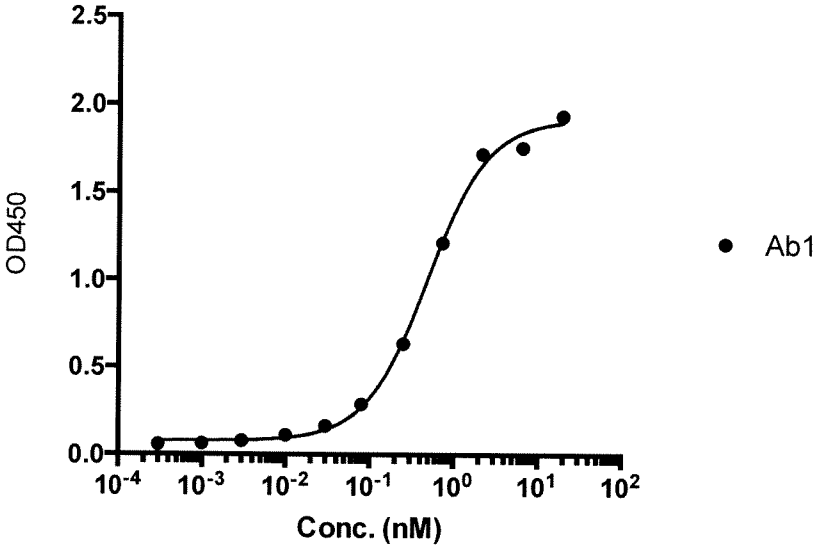
Antibody Light chain DNA features

Sequence Name	Variable region coordinates	SEQ ID NO:	CDR1 coordinates	SEQ ID NO:	CDR2 coordinates	SEQ ID NO:	CDR3 coordinates	SEQ ID NO:
Ab1	1-339	32	70-102	34	148-168	36	265-306	38
Ab2	1-339	72	70-102	74	148-168	76	265-306	78
Ab3	1-339	112	70-102	114	148-168	116	265-306	118
Ab4	1-339	152	70-102	154	148-168	156	265-306	158
Ab5	1-342	192	73-105	194	151-171	196	268-309	198
Ab6	1-342	232	73-105	234	151-171	236	268-309	238
Ab7	1-342	272	73-105	274	151-171	276	268-309	278
Ab9	1-342	312	73-105	314	151-171	316	268-309	318
Ab10	1-339	352	70-102	354	148-168	356	265-306	358
Ab11	1-339	392	70-102	394	148-168	396	265-306	398
Ab12	1-339	432	70-102	434	148-168	436	265-306	438
Ab1.H	1-339	472	70-102	474	148-168	476	265-306	478
Ab2.H	1-339	512	70-102	514	148-168	516	265-306	518
Ab3.H	1-339	552	70-102	554	148-168	556	265-306	558
Ab4.H	1-339	592	70-102	594	148-168	596	265-306	598
Ab6.H	1-339	632	70-102	634	148-168	636	265-306	638
Ab7.H	1-339	672	70-102	674	148-168	676	265-306	678
Ab7A.H	1-342	712	73-105	714	151-171	716	268-309	718
Ab10.H	1-339	752	70-102	754	148-168	756	265-306	758
Ab11.H	1-339	792	70-102	794	148-168	796	265-306	798
Ab11A.H	1-339	832	70-102	834	148-168	836	265-306	838
Ab12.H	1-339	872	70-102	874	148-168	876	265-306	878

Figure 12

Antibody Light chain DNA features

Sequence Name	FR1 coordinates	SEQ ID NO:	FR2 coordinates	SEQ ID NO:	FR3 coordinates	SEQ ID NO:	FR4 coordinates	SEQ ID NO:	Constant region coordinates	SEQ ID NO:
Ab1	1-69	33	103-147	35	169-264	37	307-339	39	340-657	40
Ab2	1-69	73	103-147	75	169-264	77	307-339	79	340-657	80
Ab3	1-69	113	103-147	115	169-264	117	307-339	119	340-657	120
Ab4	1-69	153	103-147	155	169-264	157	307-339	159	340-657	160
Ab5	1-72	193	106-150	195	172-267	197	310-342	199	343-660	200
Ab6	1-72	233	106-150	235	172-267	237	310-342	239	343-660	240
Ab7	1-72	273	106-150	275	172-267	277	310-342	279	343-660	280
Ab9	1-72	313	106-150	315	172-267	317	310-342	319	343-660	320
Ab10	1-69	353	103-147	355	169-264	357	307-339	359	340-657	360
Ab11	1-69	393	103-147	395	169-264	397	307-339	399	340-657	400
Ab12	1-69	433	103-147	435	169-264	437	307-339	439	340-657	440
Ab1.H	1-69	473	103-147	475	169-264	477	307-339	479	340-657	480
Ab2.H	1-69	513	103-147	515	169-264	517	307-339	519	340-657	520
Ab3.H	1-69	553	103-147	555	169-264	557	307-339	559	340-657	560
Ab4.H	1-69	593	103-147	595	169-264	597	307-339	599	340-657	600
Ab6.H	1-69	633	103-147	635	169-264	637	307-339	639	340-657	640
Ab7.H	1-69	673	103-147	675	169-264	677	307-339	679	340-657	680
Ab7A.H	1-72	713	106-150	715	172-267	717	310-342	719	343-660	720
Ab10.H	1-69	753	103-147	755	169-264	757	307-339	759	340-657	760
Ab11.H	1-69	793	103-147	795	169-264	797	307-339	799	340-657	800
Ab11A.H	1-69	833	103-147	835	169-264	837	307-339	839	340-657	840
Ab12.H	1-69	873	103-147	875	169-264	877	307-339	879	340-657	880



	EC50 (nM)
Ab1	0.48

FIG. 13. Ab1 recognition of human ACTH.

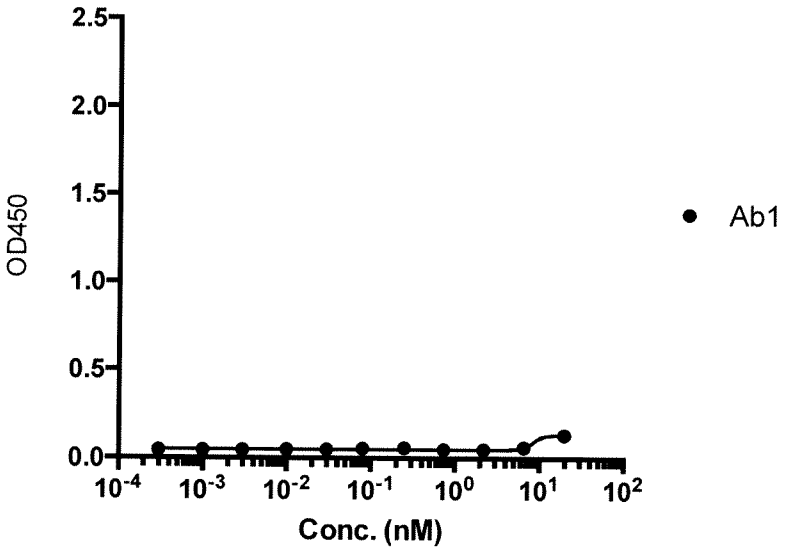
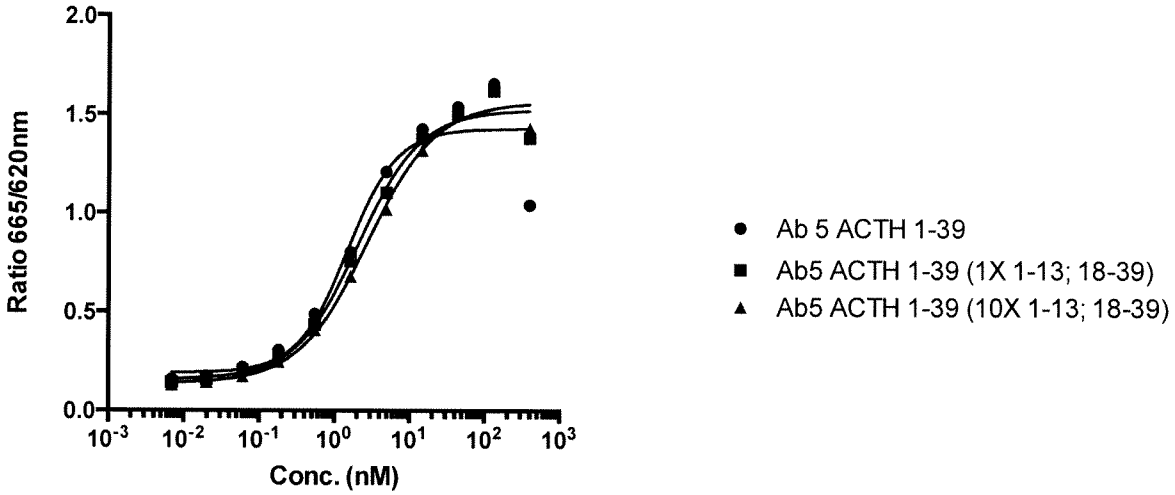
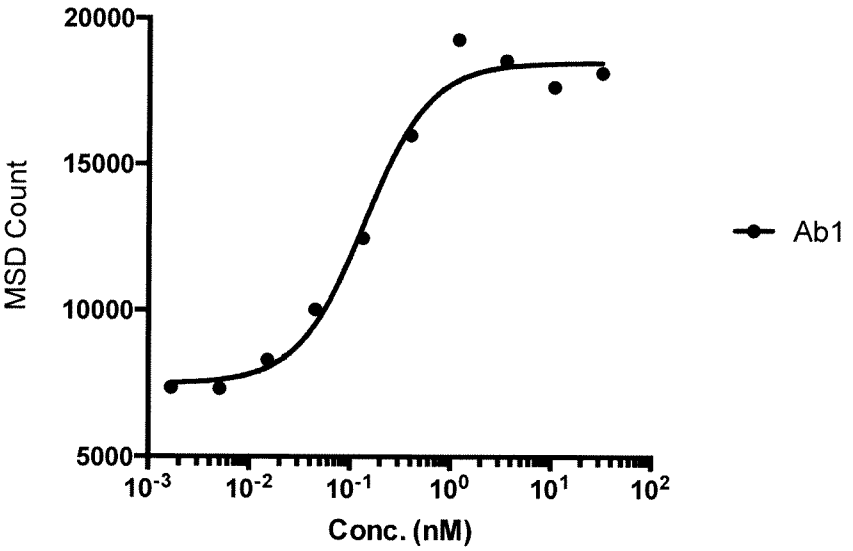


FIG. 14. Lack of recognition of human ACTH 1-13 and 18-39.



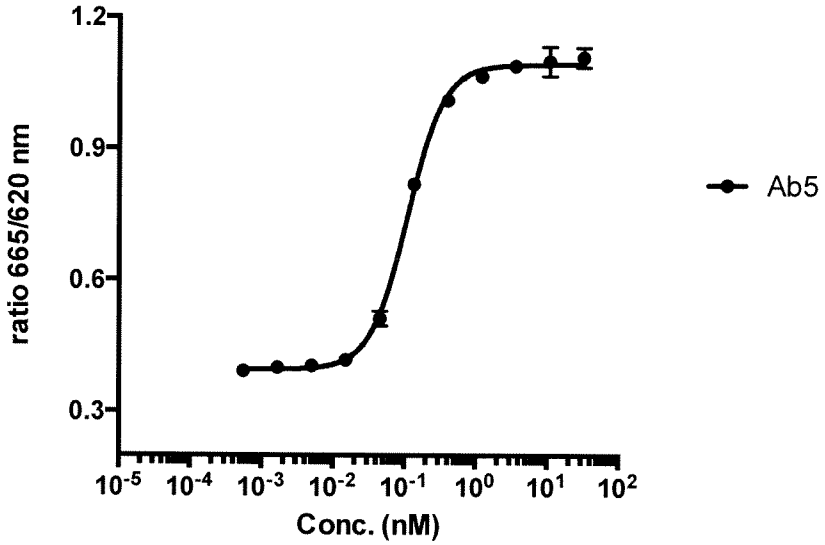
	EC50 (nM)
Ab5	1.50

FIG. 15. Recognition of human ACTH 1-39 and lack of recognition of human ACTH 1-13 and 18-39.



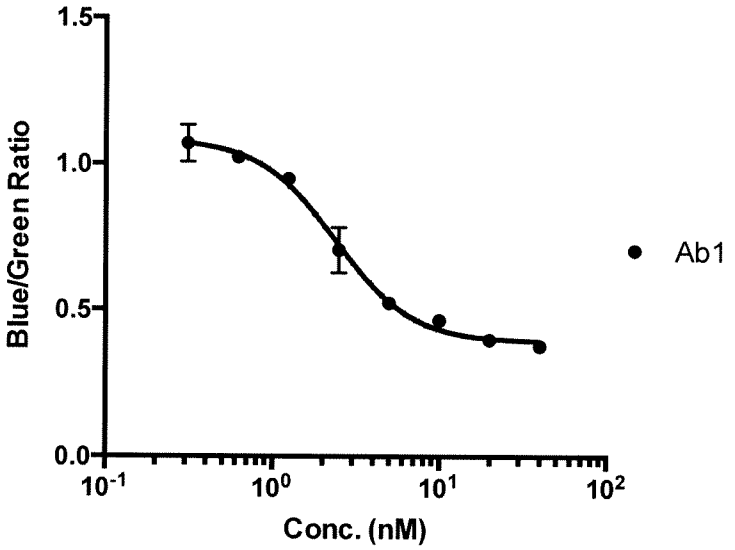
	IC50 (nM)
Ab1	0.14

FIG. 16. Inhibition of ACTH driven cAMP production in MC2R expressing cells



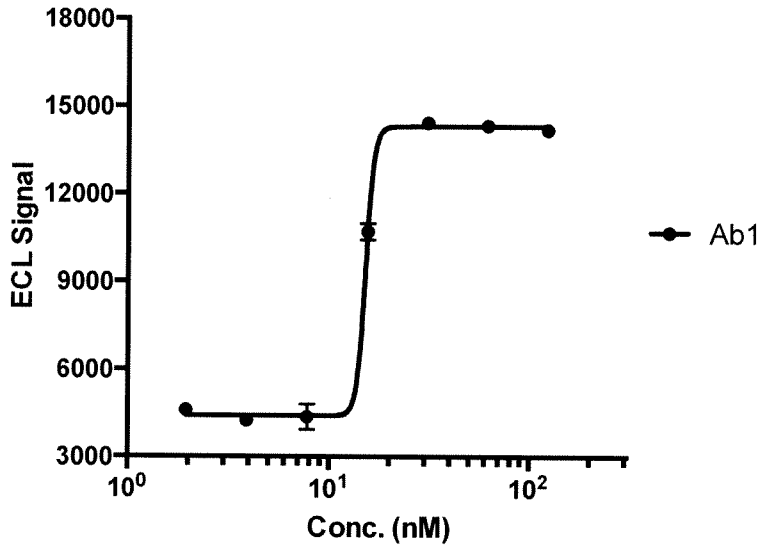
	IC50 (nM)
Ab5	0.11

FIG. 17. Inhibition of ACTH driven cAMP production in MC2R expressing cells



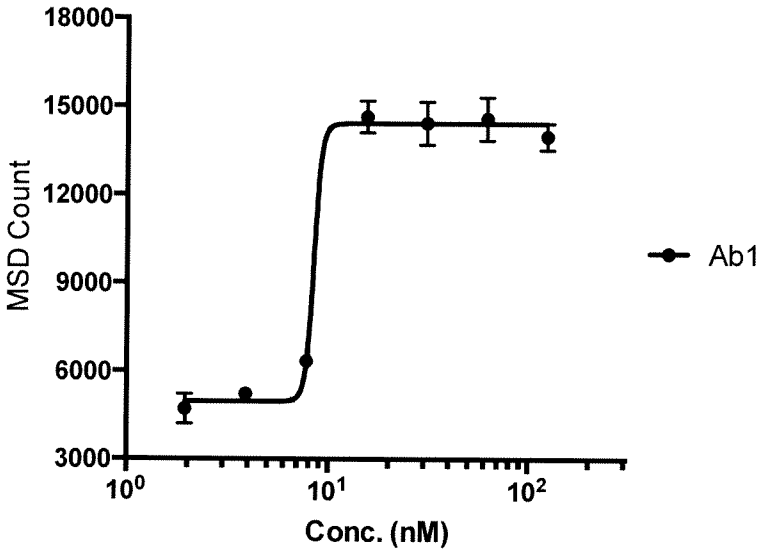
	IC50 (nM)
Ab1	2.38

FIG. 18. Inhibition of ACTH driven cAMP production in MC1R expressing cells



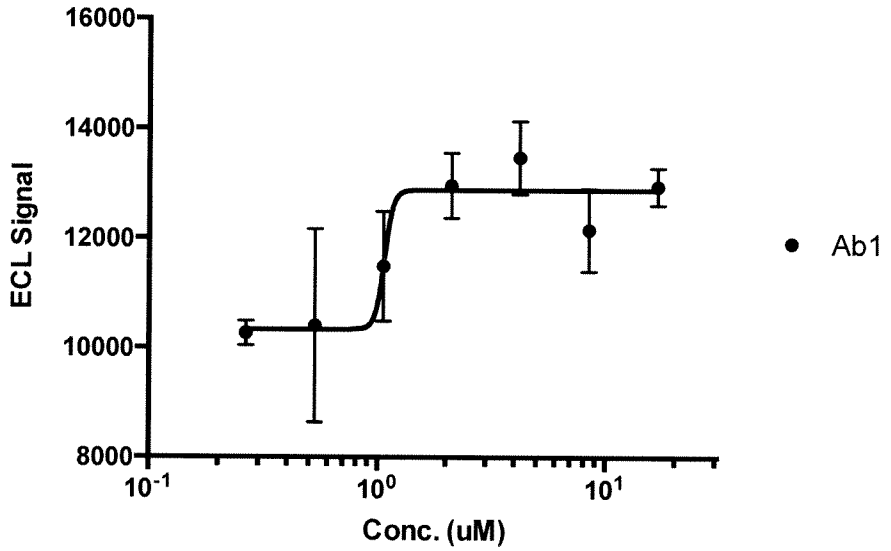
	IC50 (nM)
Ab1	101.0

FIG. 19. Inhibition of ACTH driven cAMP production in MC3R expressing cells



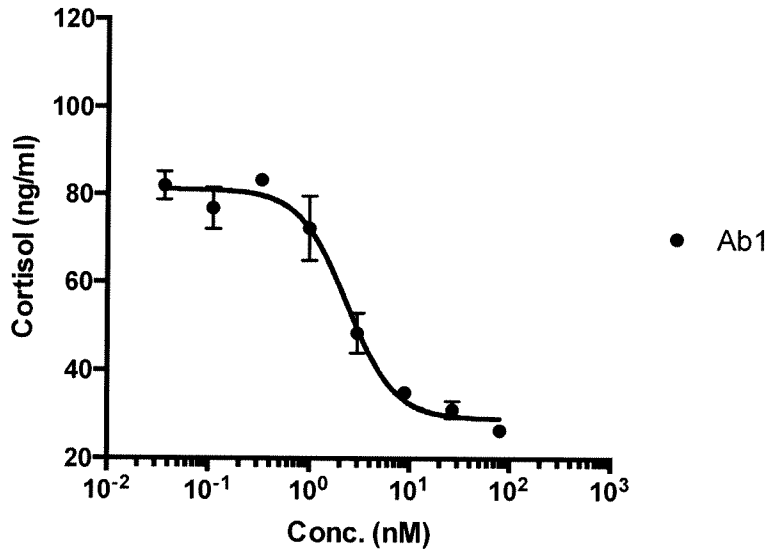
	IC50 (nM)
Ab1	56.4

FIG. 20. Inhibition of ACTH driven cAMP production in MC4R expressing cells



	IC50 (uM)
Ab1	1.1

FIG. 21. Inhibition of ACTH driven cAMP production in MC5R expressing cells



	IC50 (nM)
Ab1	2.36

FIG. 22. Inhibition of ACTH driven cortisol production in Y1 cells

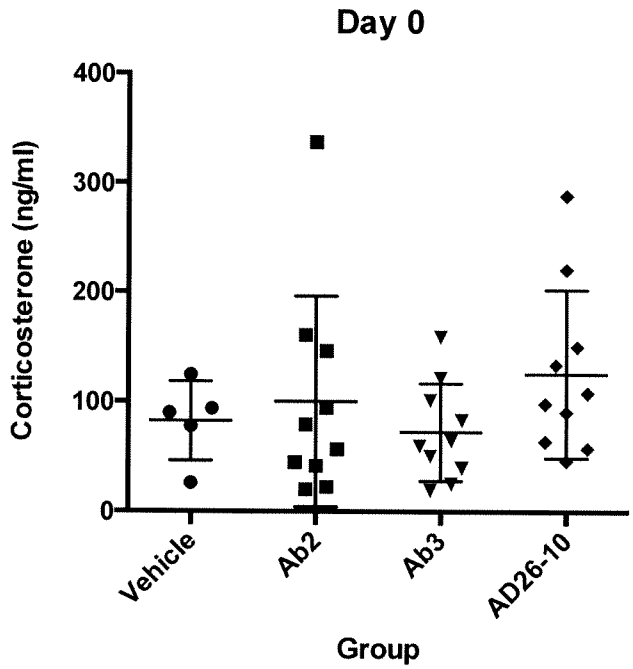


FIG. 23. Plasma corticosterone levels pre-dose

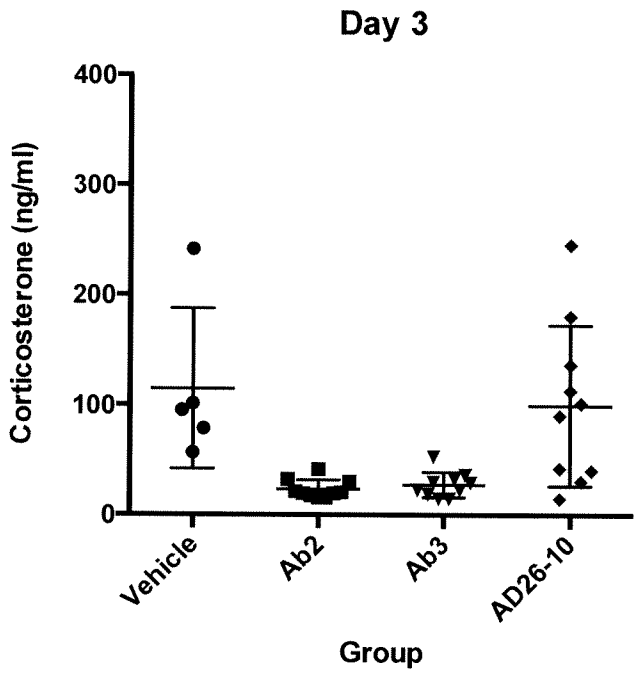


FIG. 24. Plasma corticosterone levels 48 hours post 1st dose

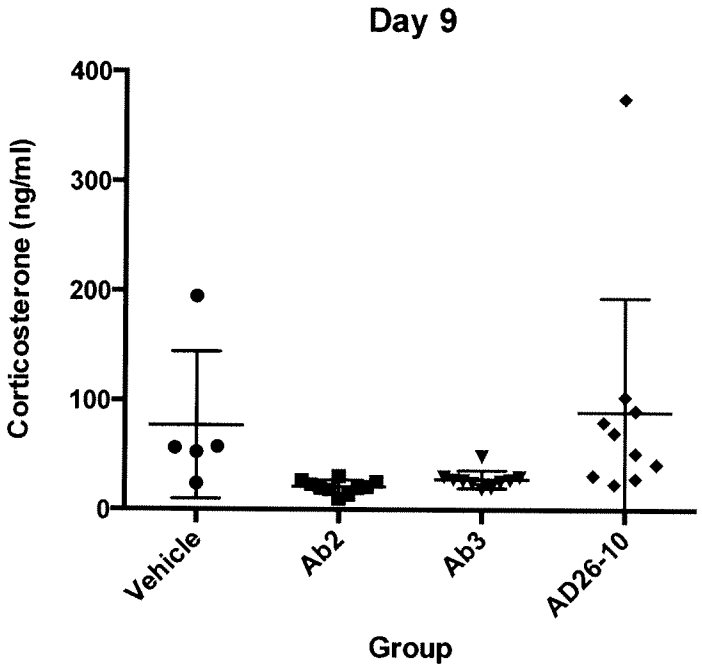


FIG. 25. Plasma corticosterone levels 48 hours post 2nd dose

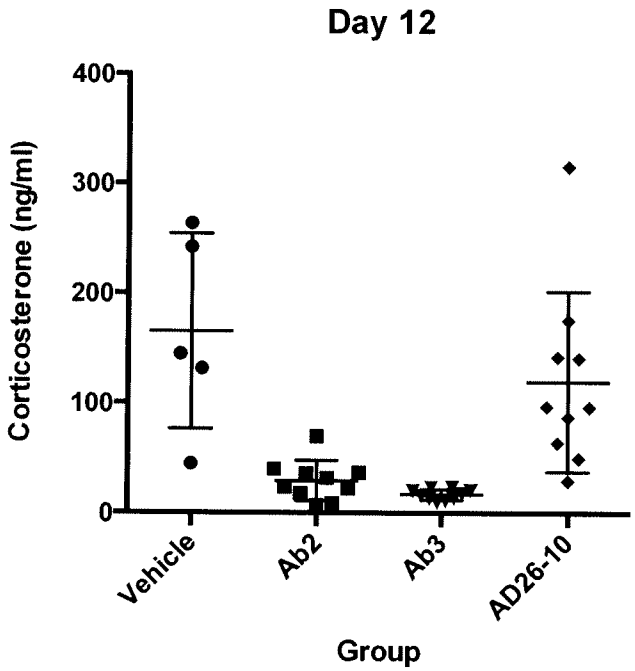
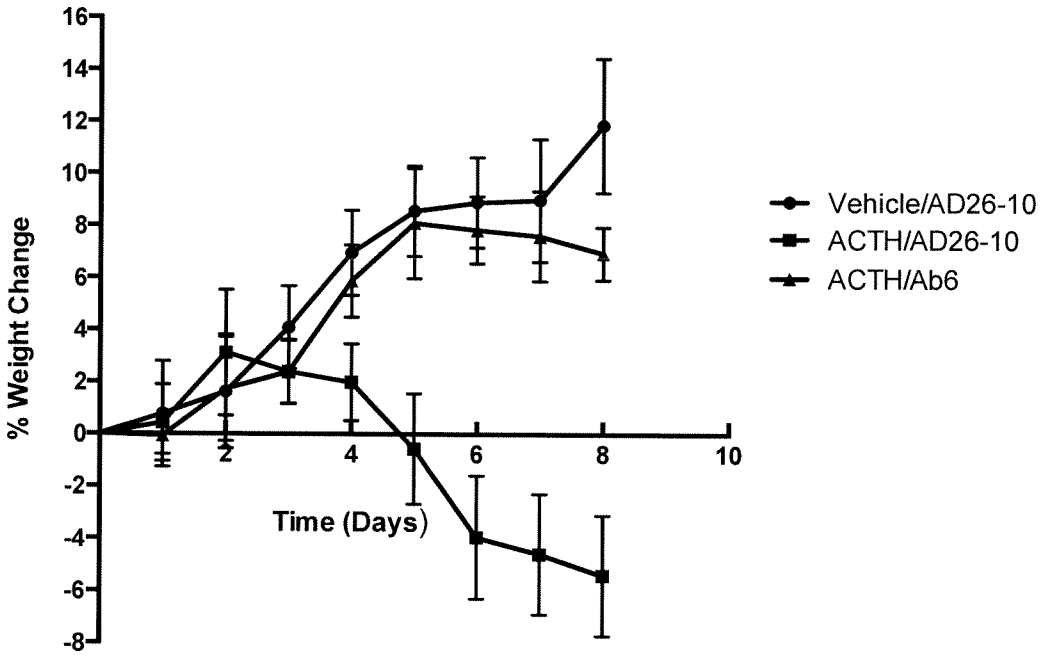


FIG. 26. Plasma corticosterone levels 120 hours post 2nd dose



ANOVA Day 8: Vehicle/AD26-10 to ACTH/AD26-10 = <0.0001
ANOVA Day 8: ACTH/Ab6 to ACTH/AD26-10 = <0.0001

FIG. 27. Percent change in animal weight

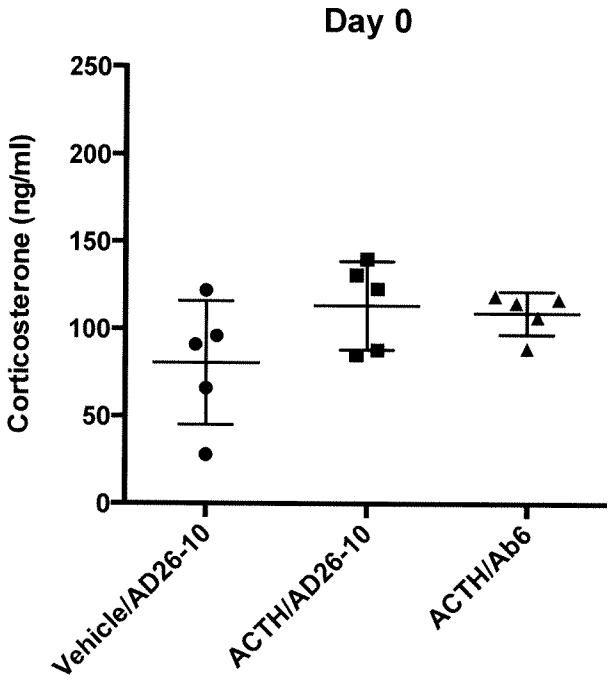


FIG. 28. Plasma corticosterone levels pre-ACTH and Ab dose

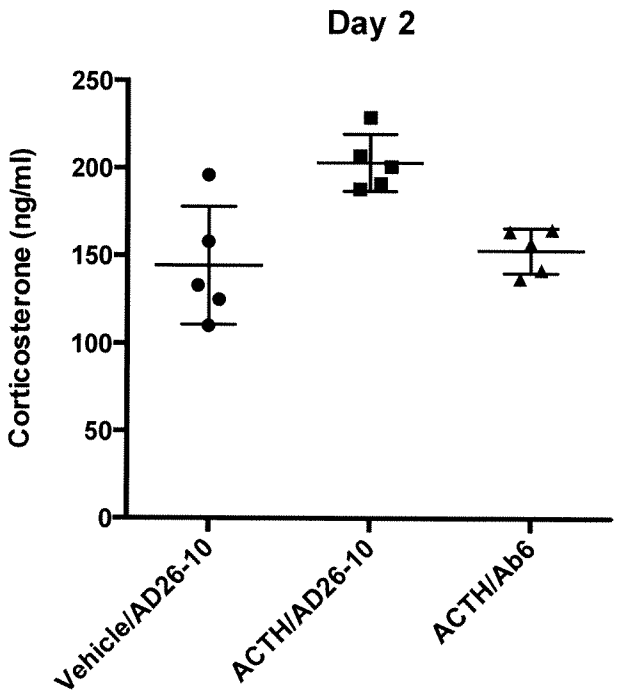


FIG. 29. Plasma corticosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

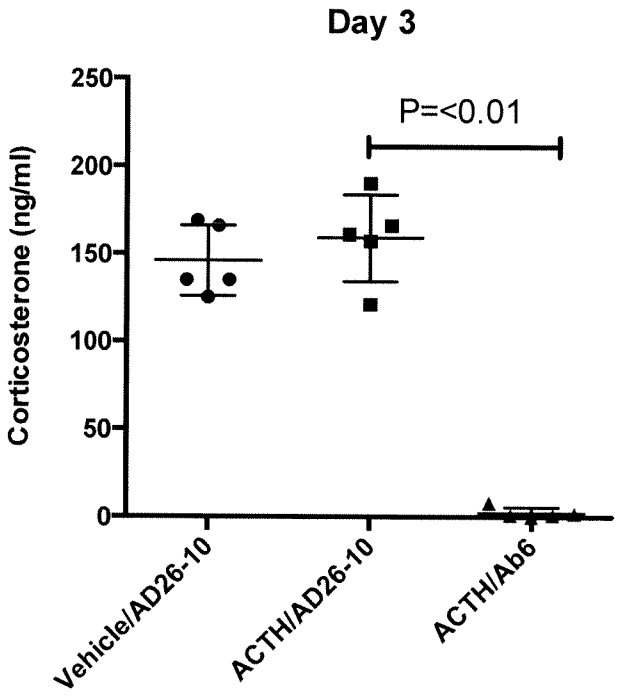


FIG. 30. Plasma corticosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

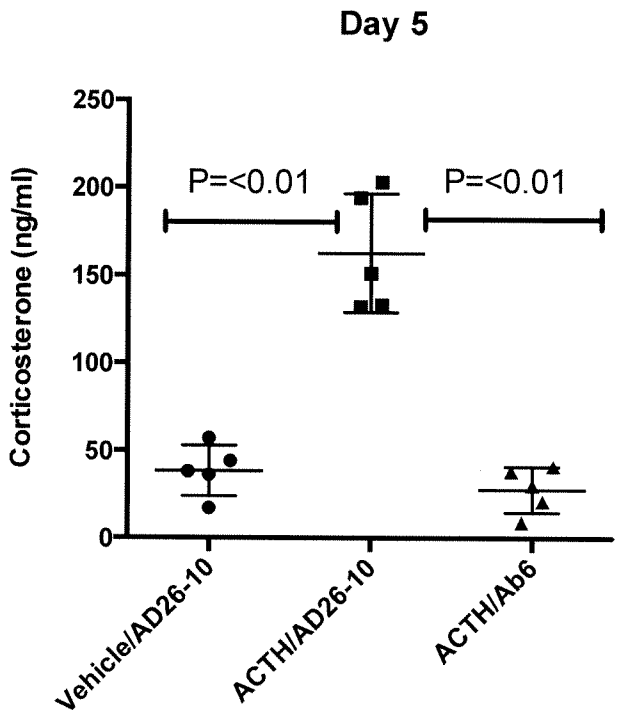


FIG. 31. Plasma corticosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

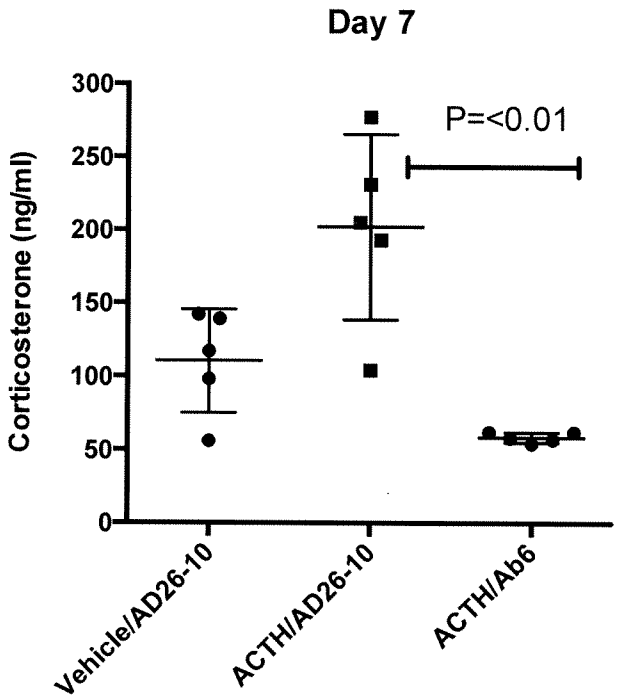


FIG. 32. Plasma corticosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose

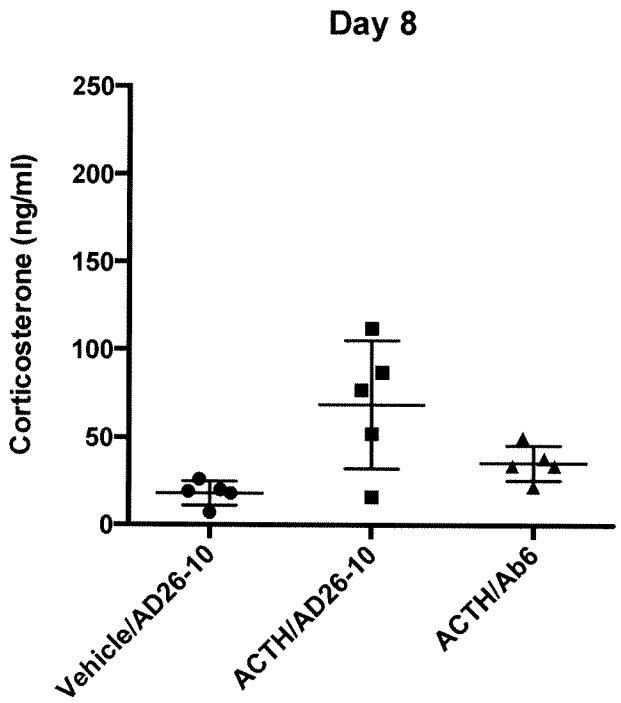


FIG. 33. Plasma corticosterone levels 168 hours post initiation of ACTH dosing and 144 hours post Ab dose

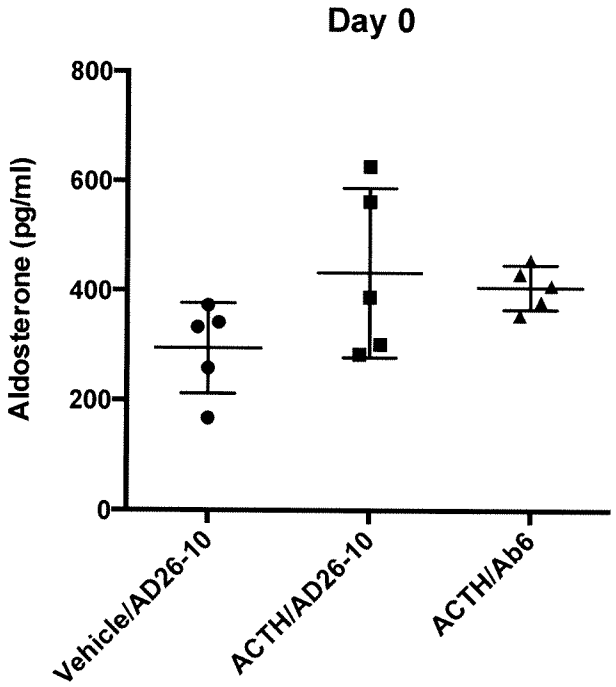


FIG. 34. Plasma aldosterone levels pre-ACTH and Ab dose

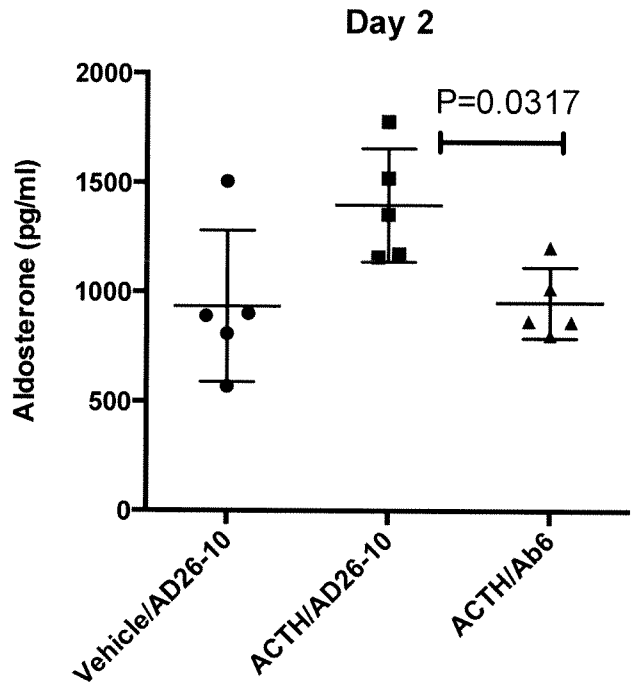


FIG. 35. Plasma aldosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

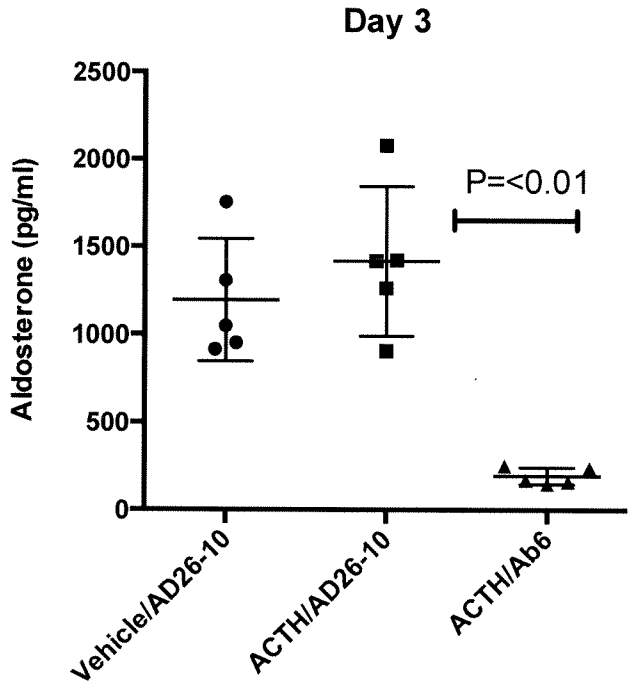


FIG. 36. Plasma aldosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

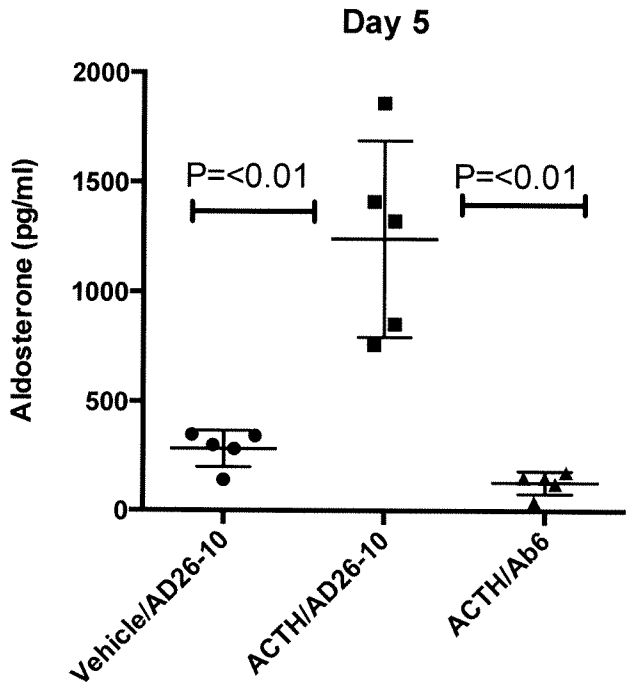


FIG. 37. Plasma aldosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

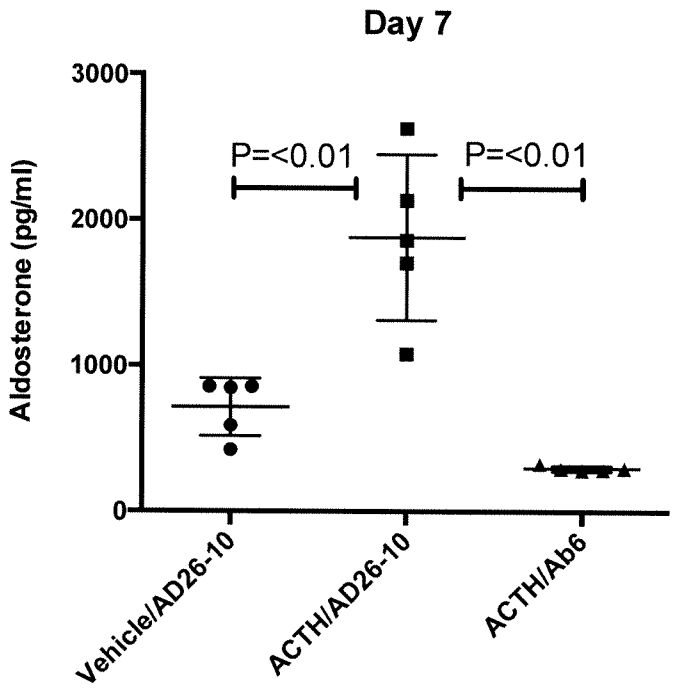


FIG. 38. Plasma aldosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose

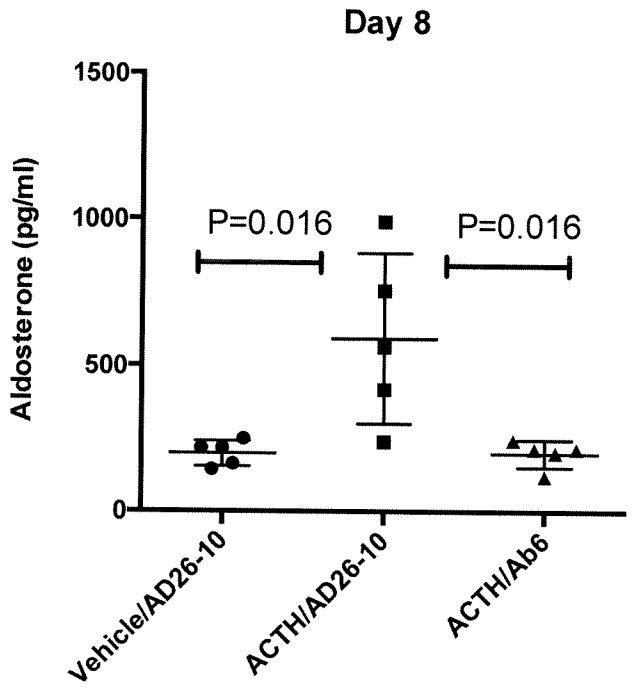


FIG. 39. Plasma aldosterone levels 168 hours post initiation of ACTH dosing and 144 hours post Ab dose

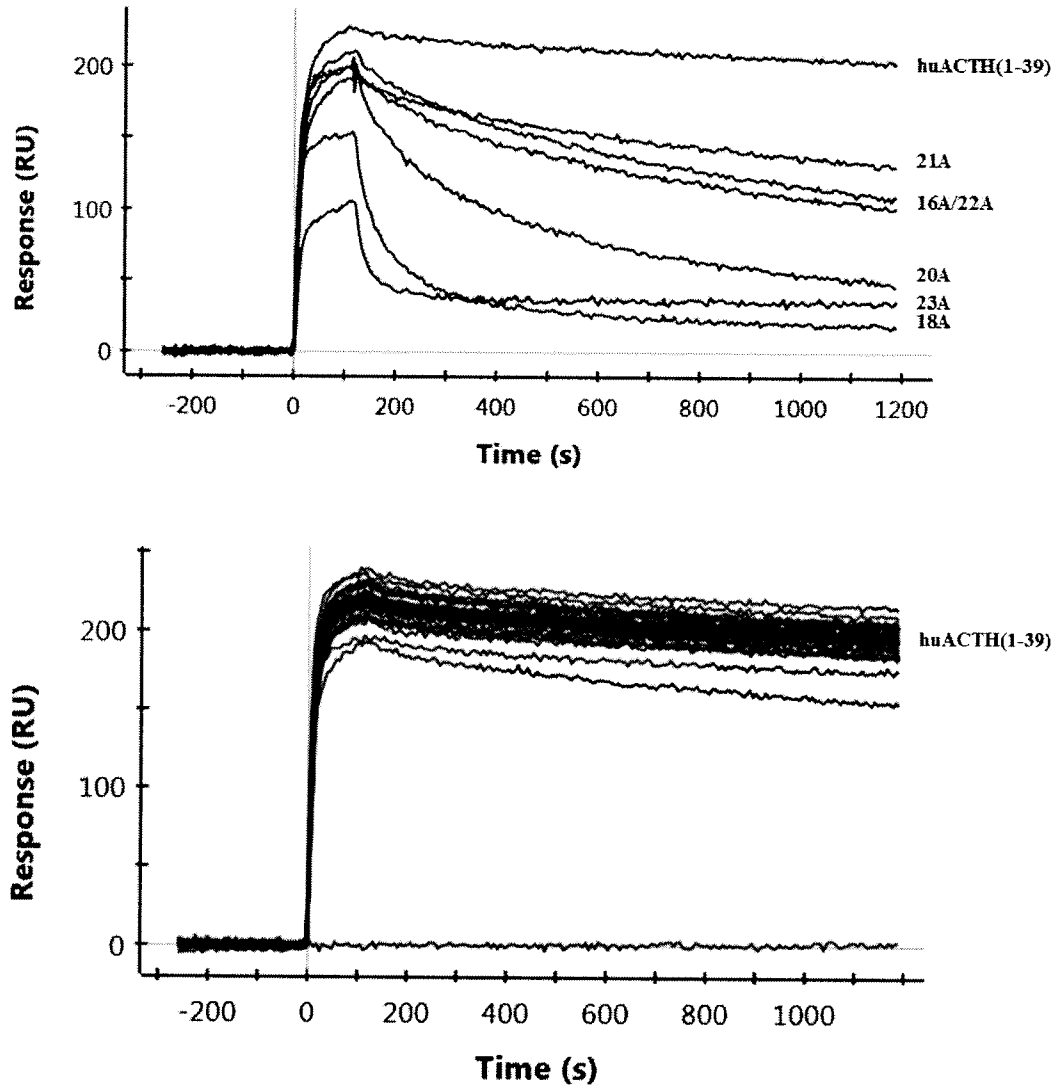


FIG. 40A. Binding kinetics of Ala mutants with Ab1.H

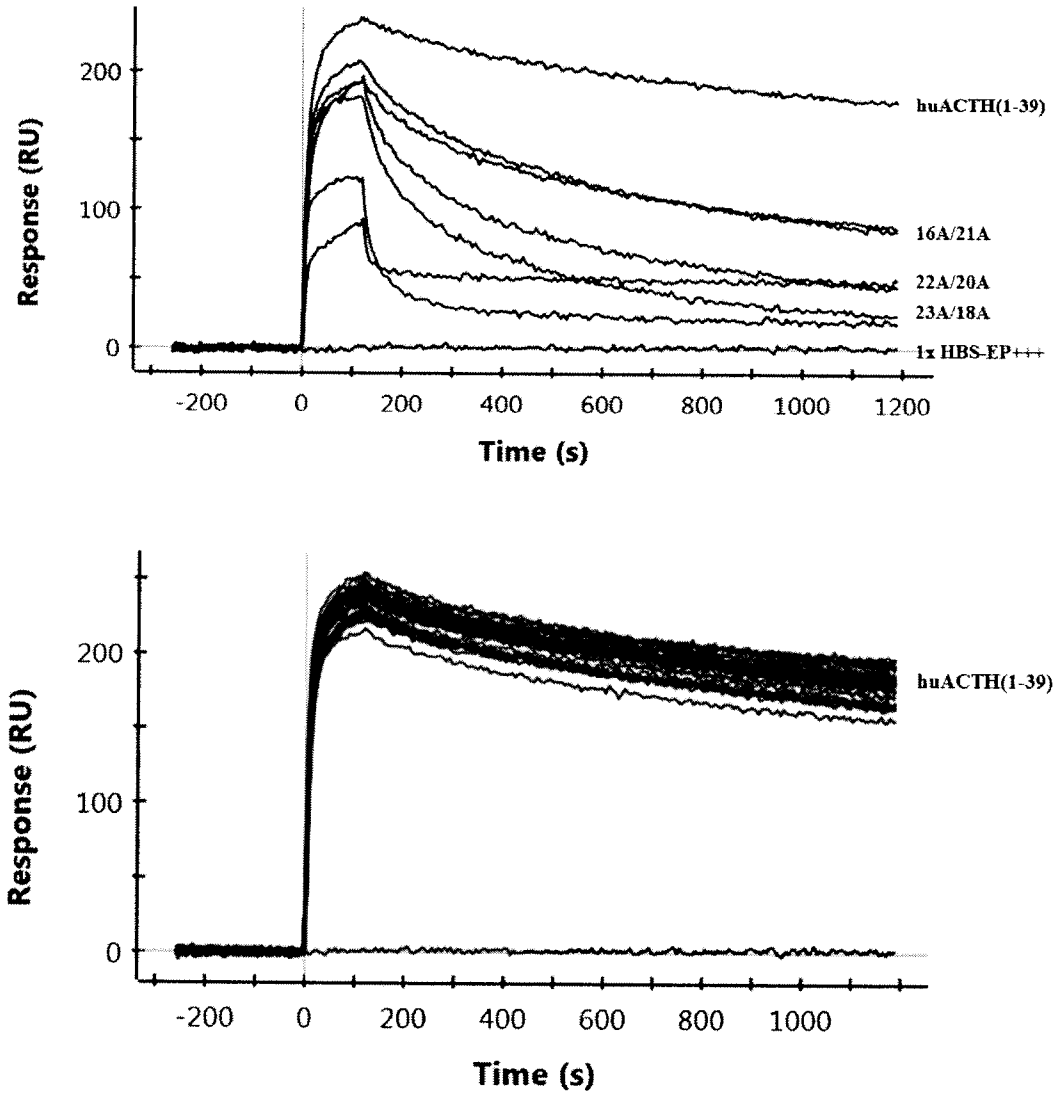


FIG. 40B. Binding kinetics of Ala mutants with Ab2.H

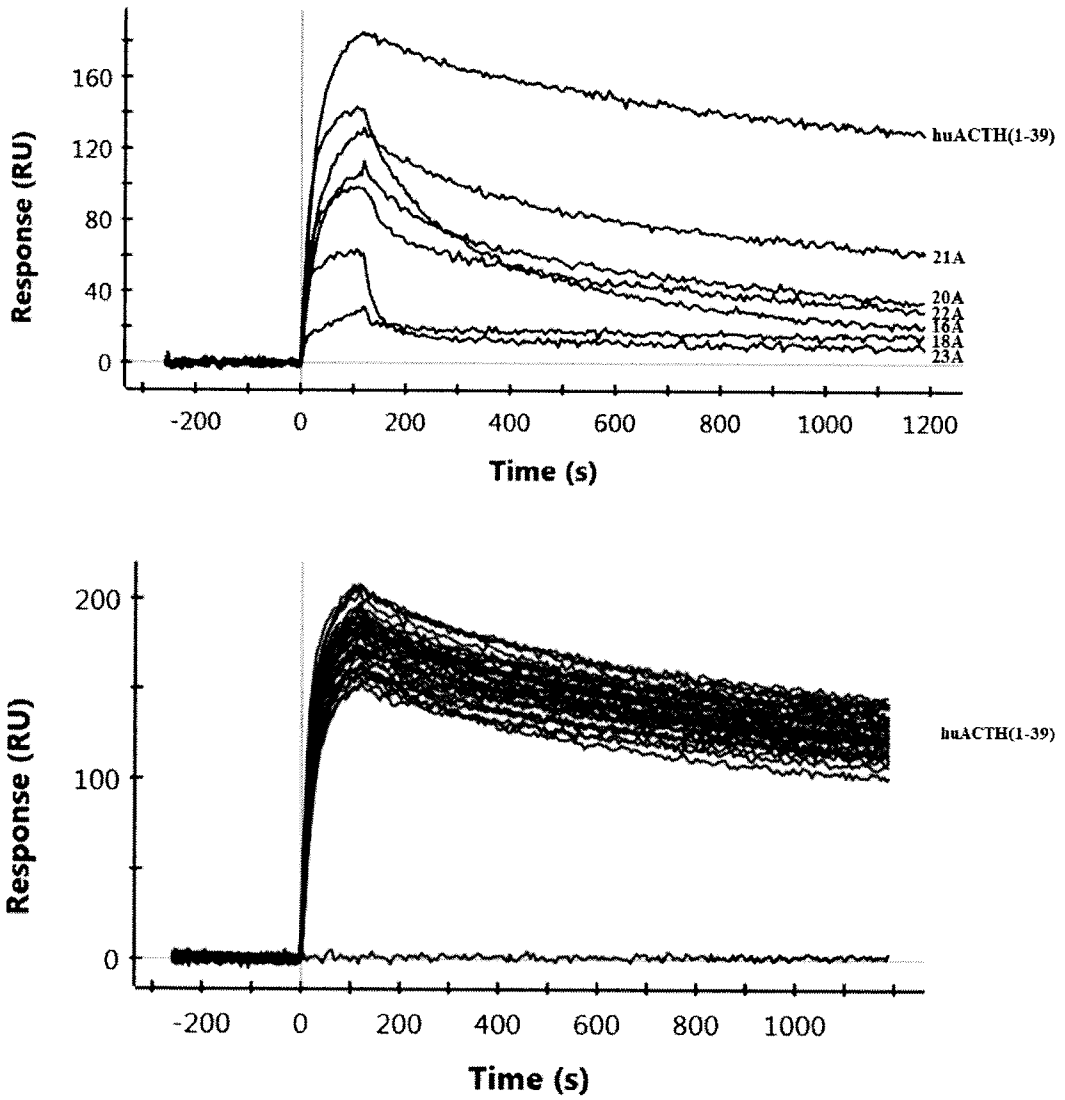


FIG. 40C. Binding kinetics of Ala mutants with Ab3.H

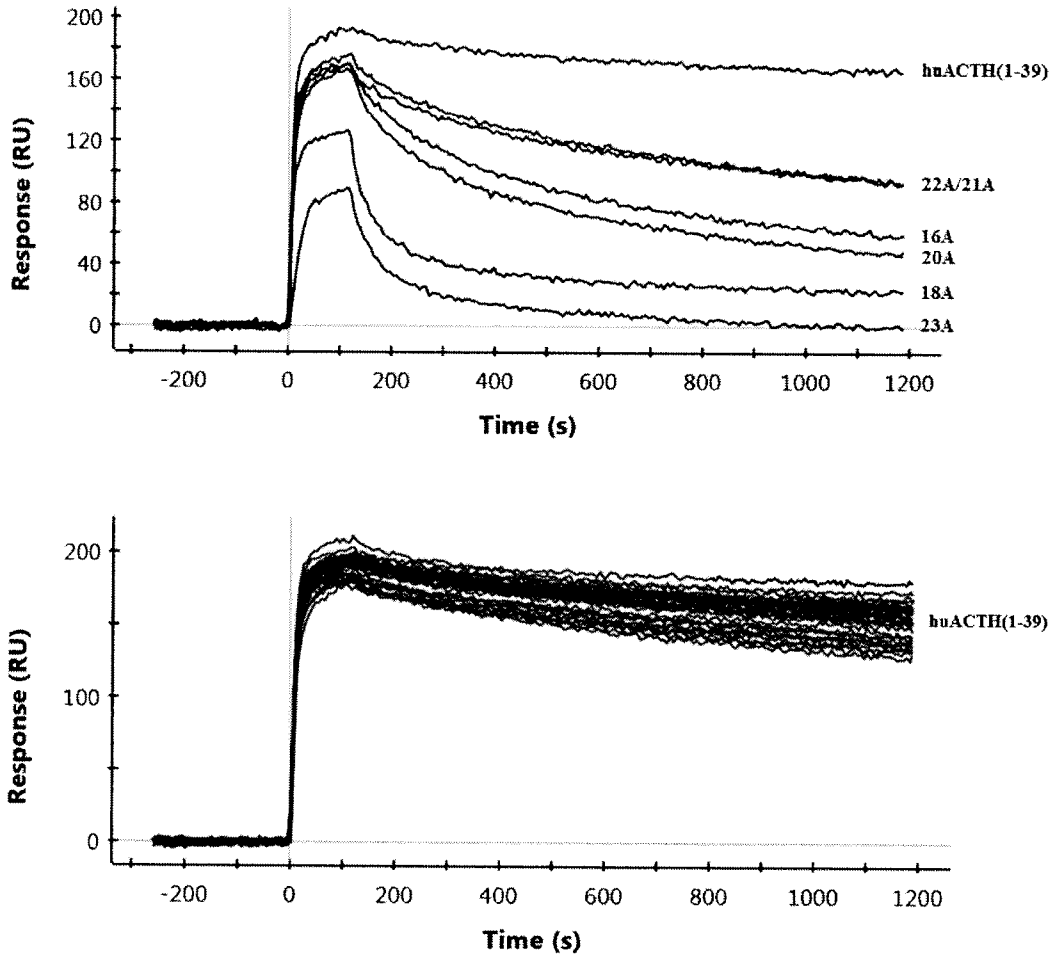


FIG. 40D. Binding kinetics of Ala mutants with Ab4.H

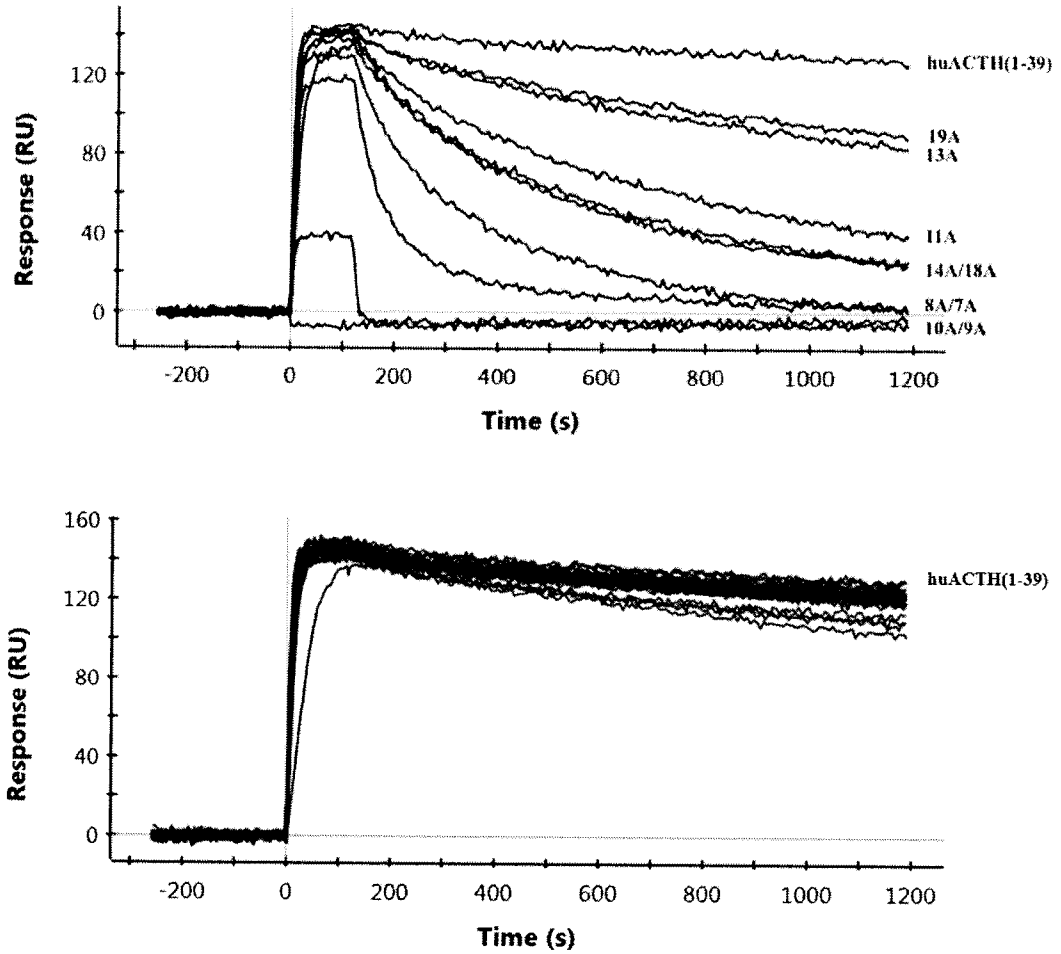


FIG. 40E. Binding kinetics of Ala mutants with Ab5

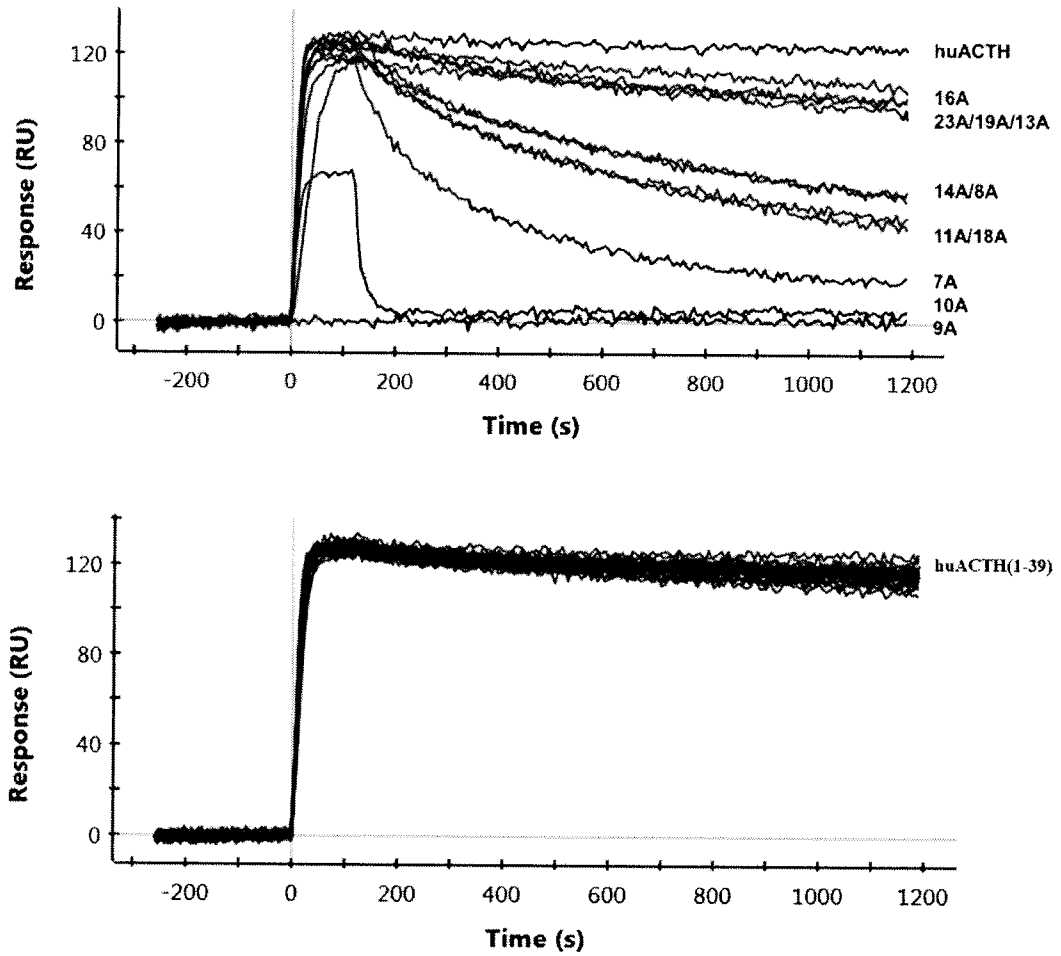


FIG. 40F. Binding kinetics of Ala mutants with Ab6.H

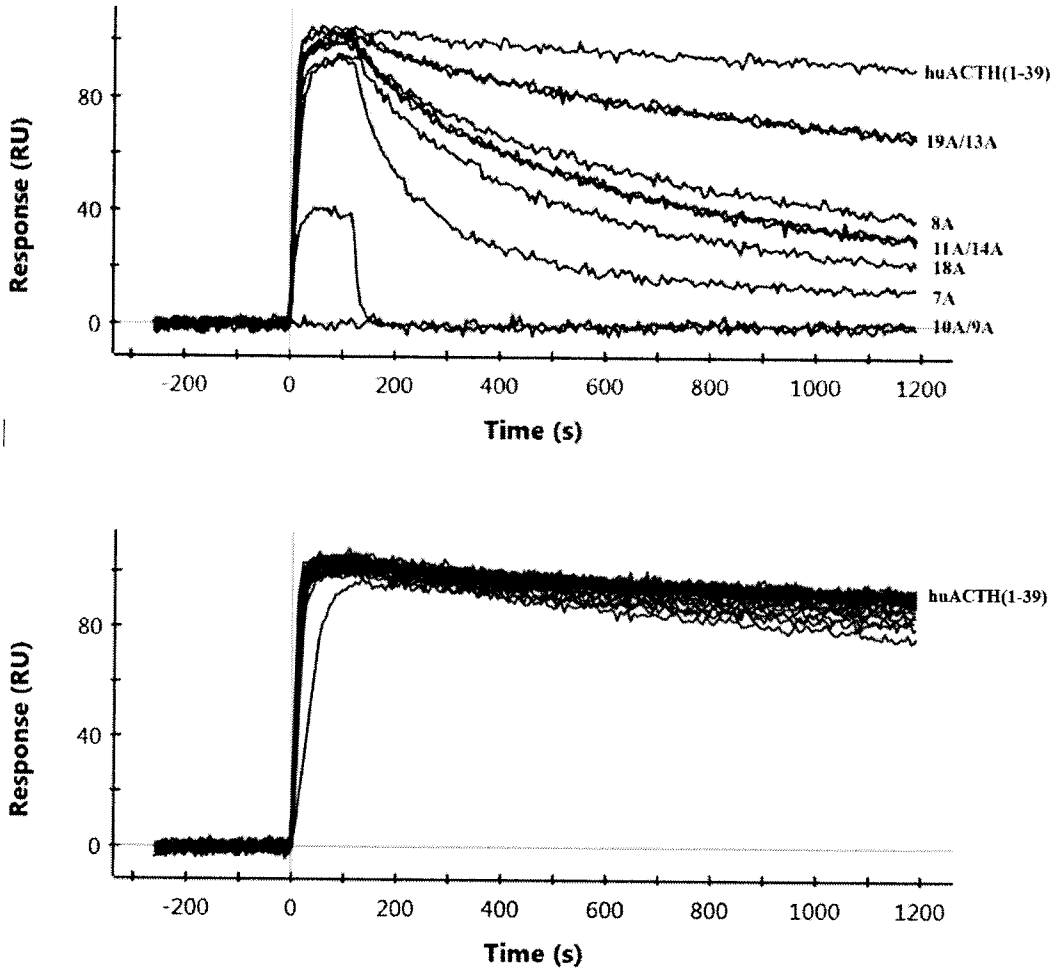


FIG. 40G. Binding kinetics of Ala mutants with Ab7.H

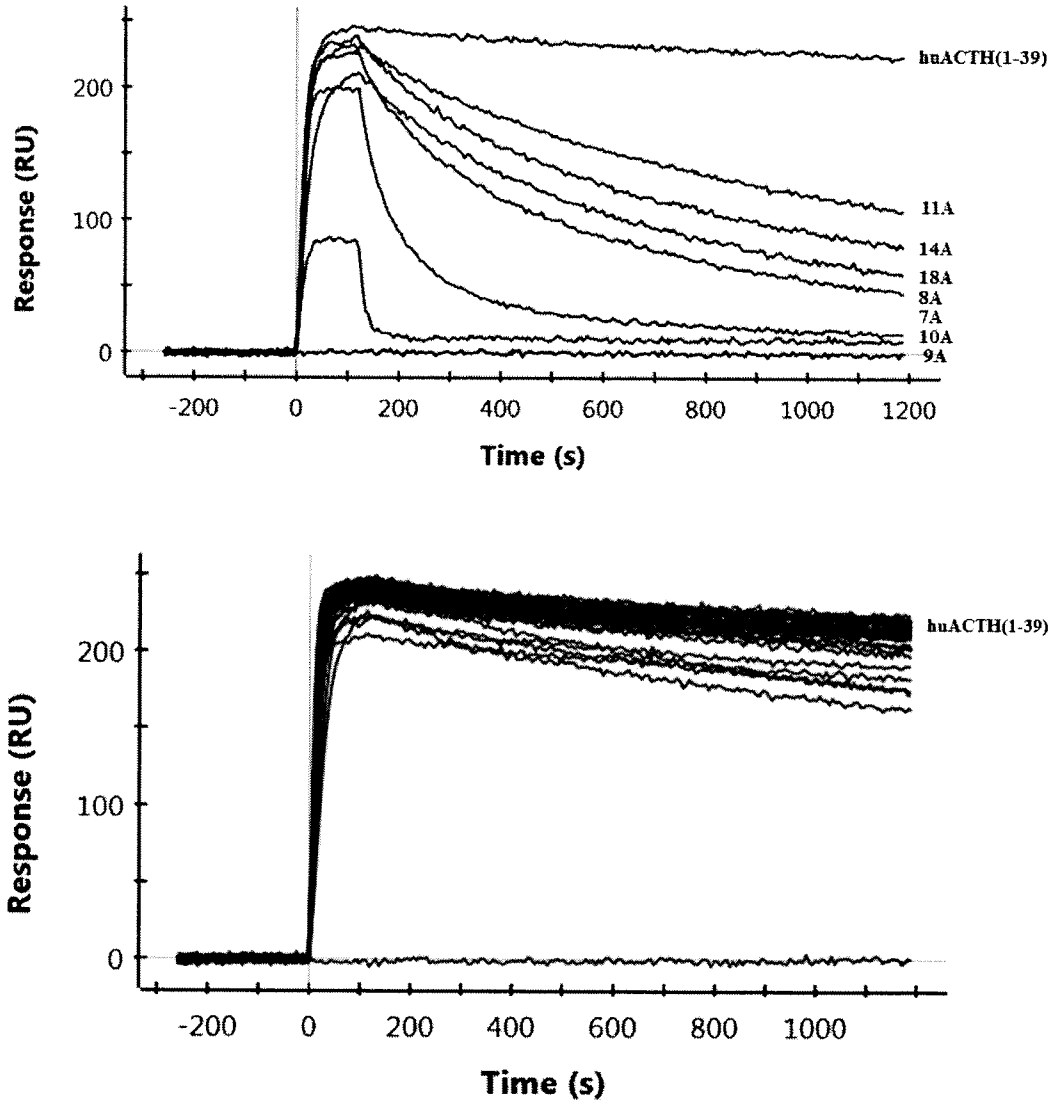


FIG. 40H. Binding kinetics of Ala mutants with Ab9

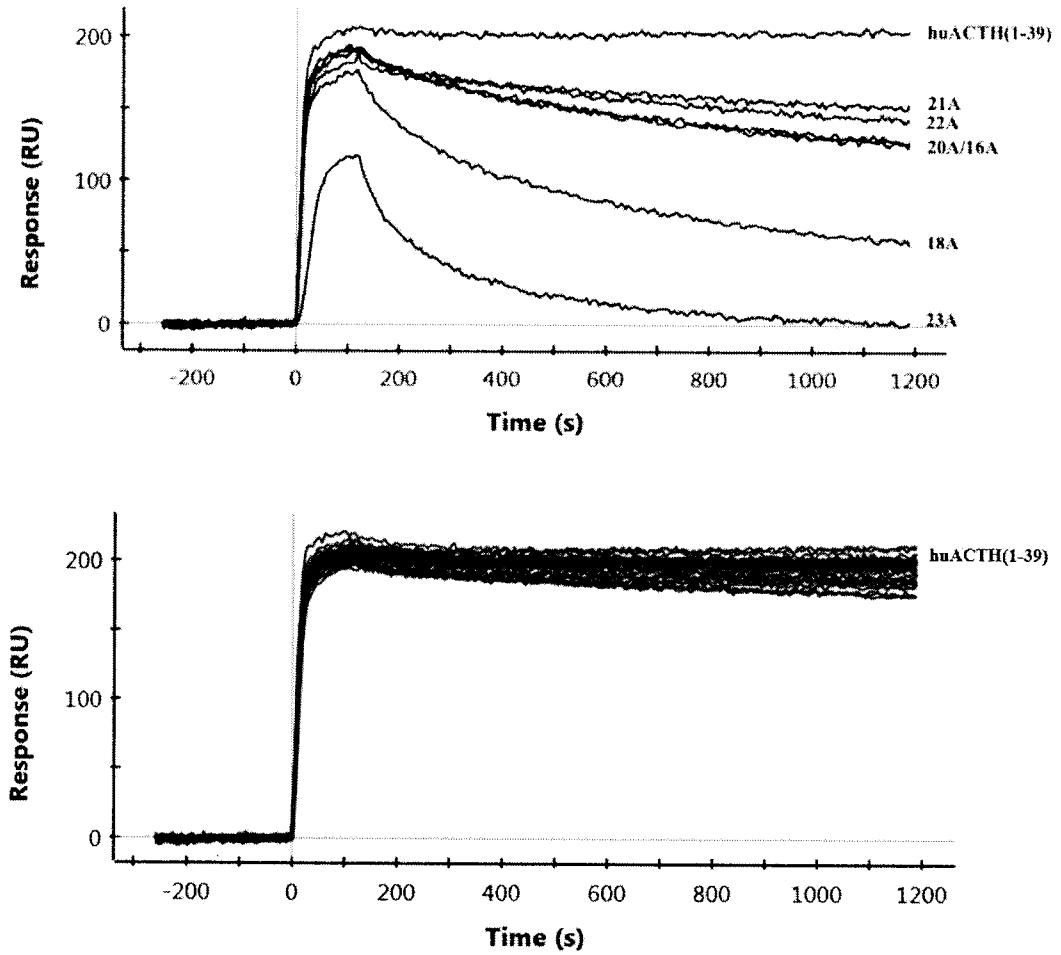


FIG. 40l. Binding kinetics of Ala mutants with Ab10.H

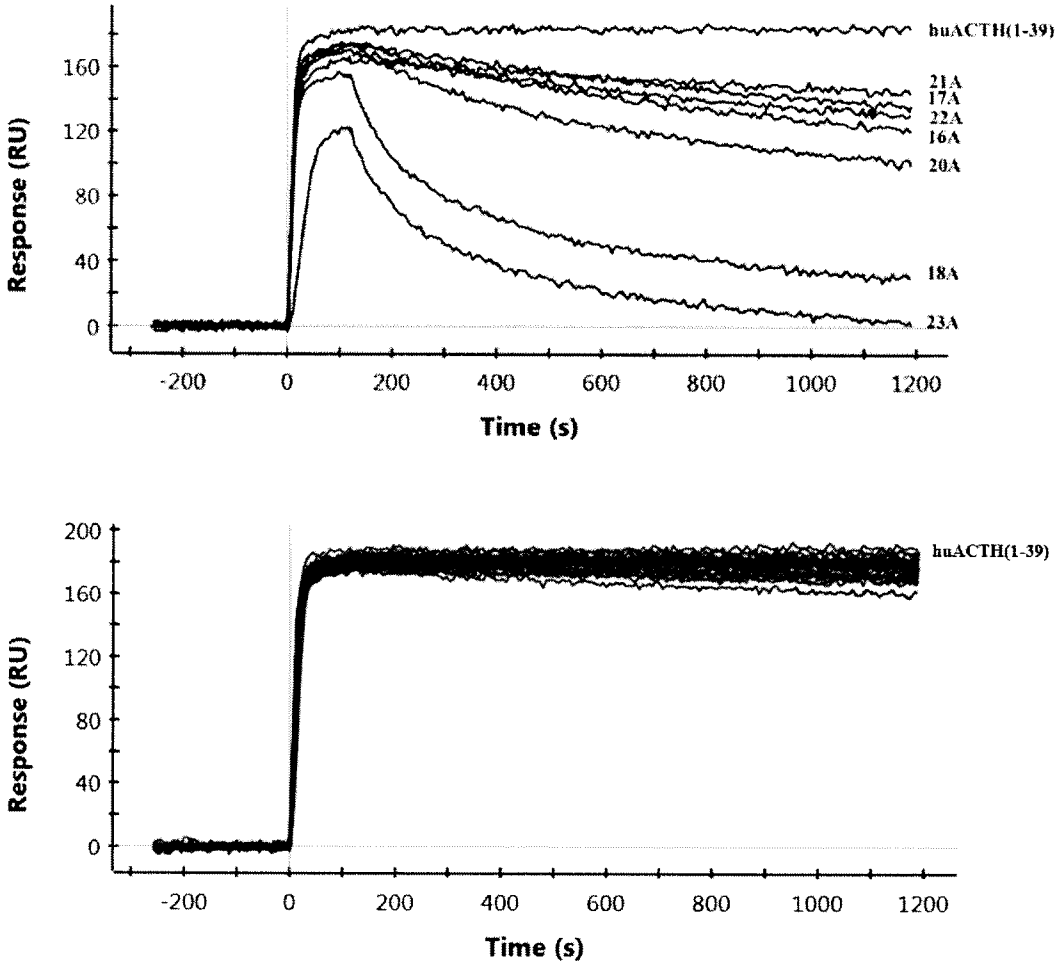


FIG. 40J. Binding kinetics of Ala mutants with Ab11.H

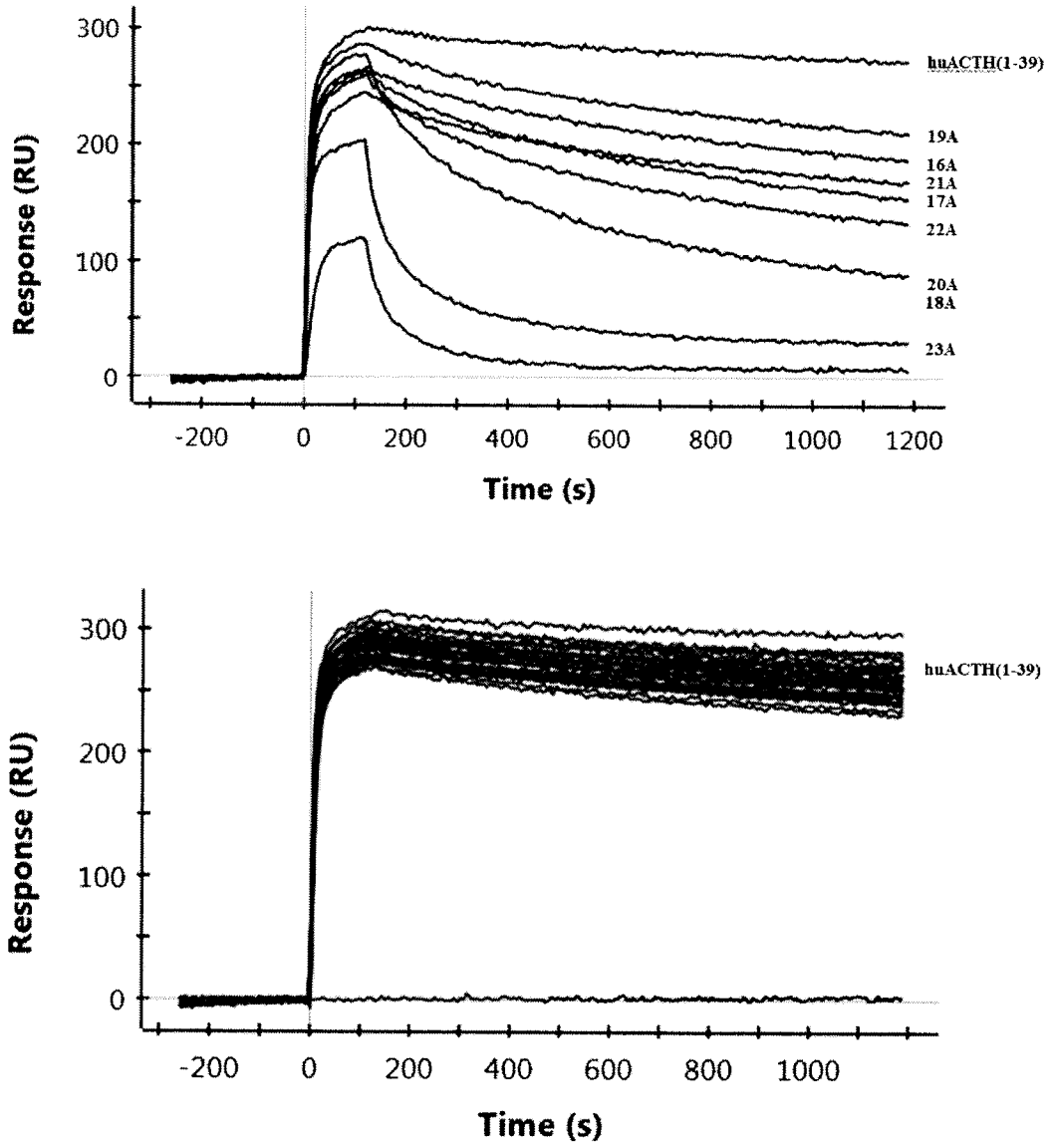


FIG. 40K. Binding kinetics of Ala mutants with Ab11A.H

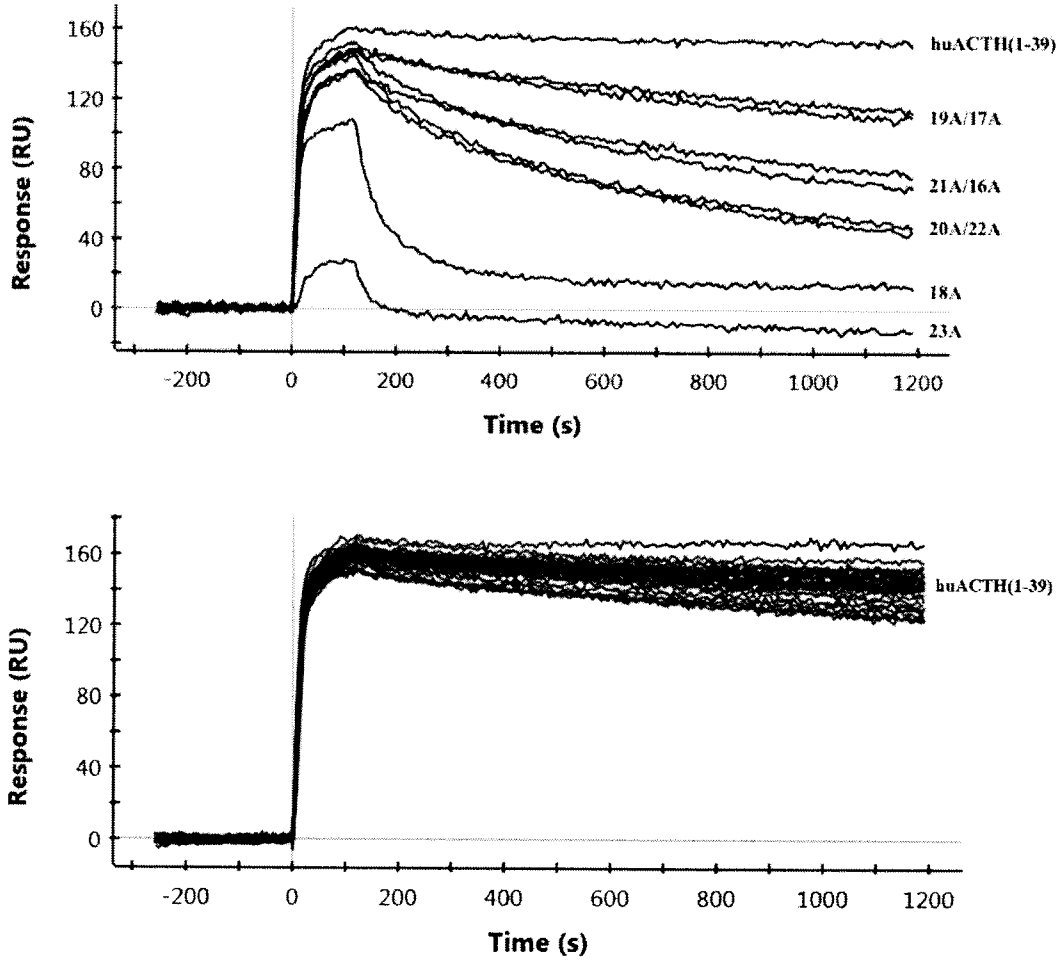
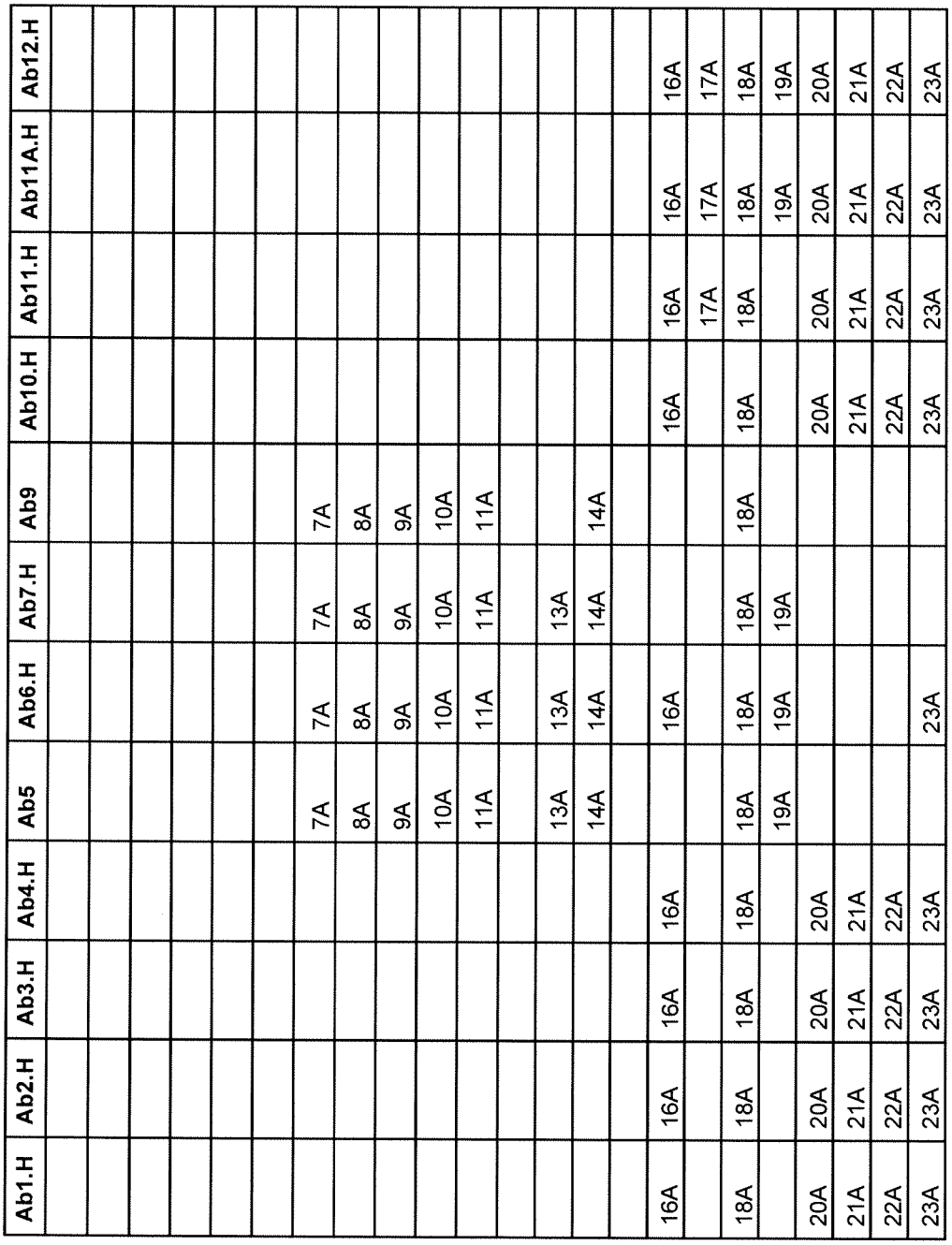


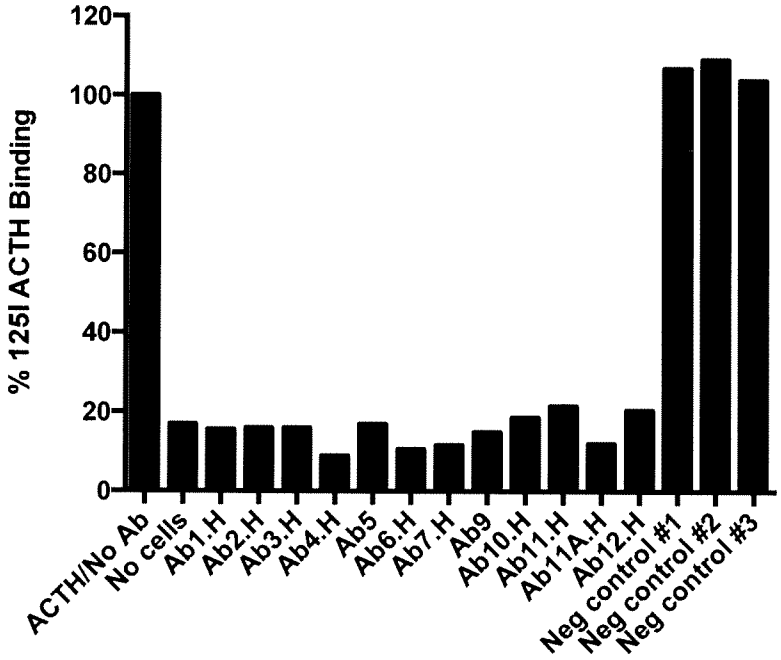
FIG. 40L. Binding kinetics of Ala mutants with Ab12.H

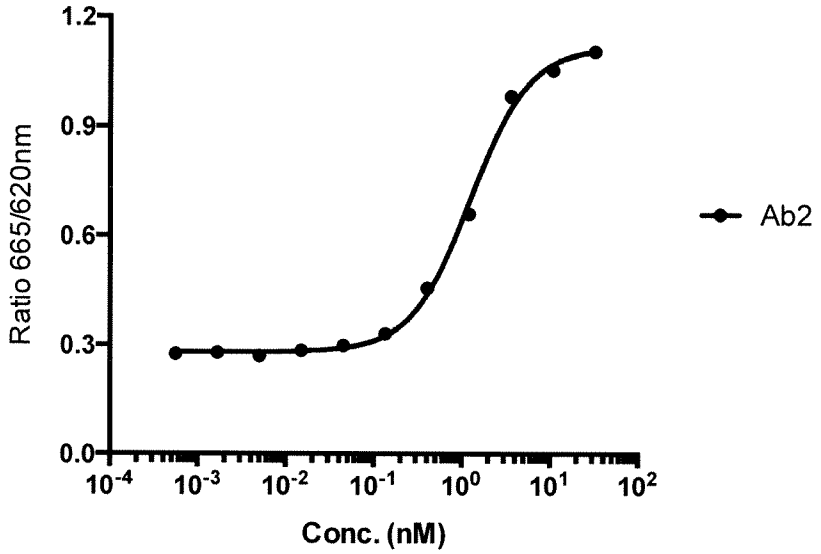
FIG. 41



Ab1.H	Ab2.H	Ab3.H	Ab4.H	Ab5	Ab6.H	Ab7.H	Ab9	Ab10.H	Ab11.H	Ab11A.H	Ab12.H
				7A	7A	7A	7A				
				8A	8A	8A	8A				
				9A	9A	9A	9A				
				10A	10A	10A	10A				
				11A	11A	11A	11A				
				13A	13A	13A					
				14A	14A	14A	14A				
16A	16A	16A	16A		16A			16A	16A	16A	16A
									17A	17A	17A
18A	18A	18A	18A	18A	18A	18A	18A	18A	18A	18A	18A
				19A	19A	19A				19A	19A
20A	20A	20A	20A					20A	20A	20A	20A
21A	21A	21A	21A					21A	21A	21A	21A
22A	22A	22A	22A					22A	22A	22A	22A
23A	23A	23A	23A		23A			23A	23A	23A	23A

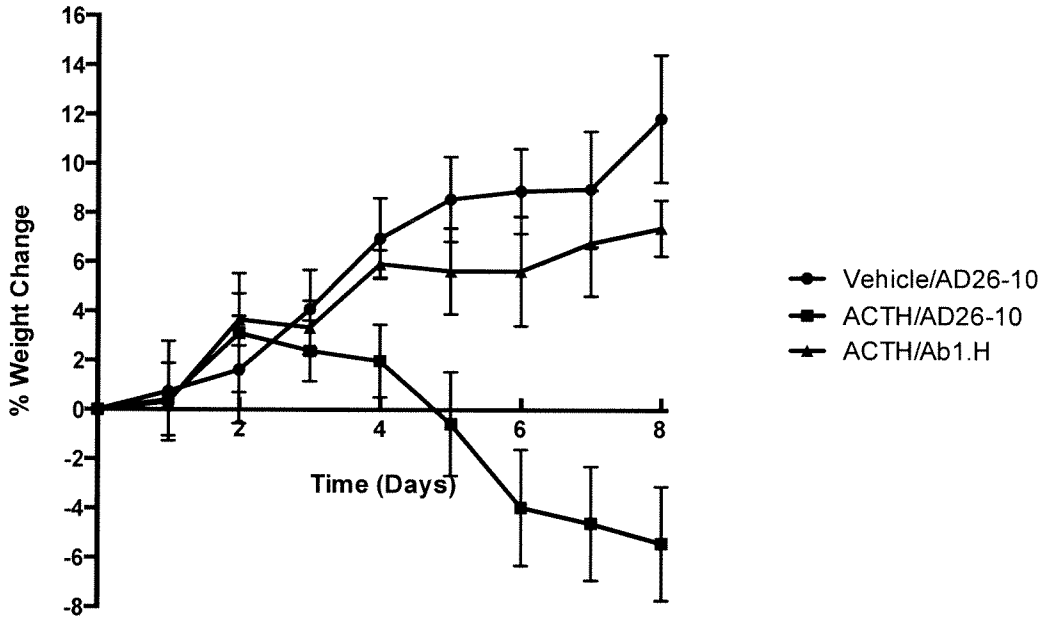
FIG. 42


% 125I ACTH Binding
120
100
80
60
40
20
0
ACTH/No Ab
No cells
Ab1.H
Ab2.H
Ab3.H
Ab4.H
Ab5
Ab6.H
Ab7.H
Ab9
Ab10.H
Ab11.H
Ab11A.H
Ab12.H
Neg control #1
Neg control #2
Neg control #3



	IC50 (nM)
Ab2	1.3

FIG. 43. Representative data showing neutralization of ACTH 1-24 induced signaling via MC2R by Ab2.



ANOVA Day 8: ACTH/Ab1.H to ACTH/AD26-10 = <0.0001

FIG. 44. Percent change in animal weight in rats receiving ACTH and Ab1.H or an isotype control.

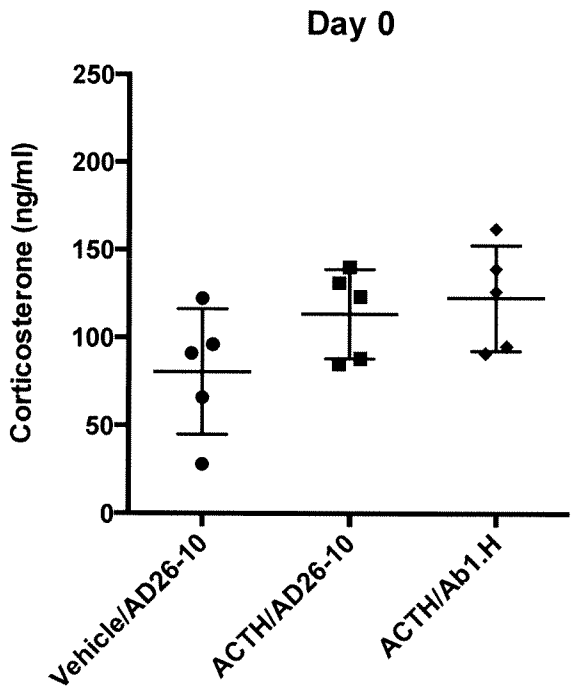


FIG. 45. Plasma corticosterone levels pre-ACTH and Ab dose

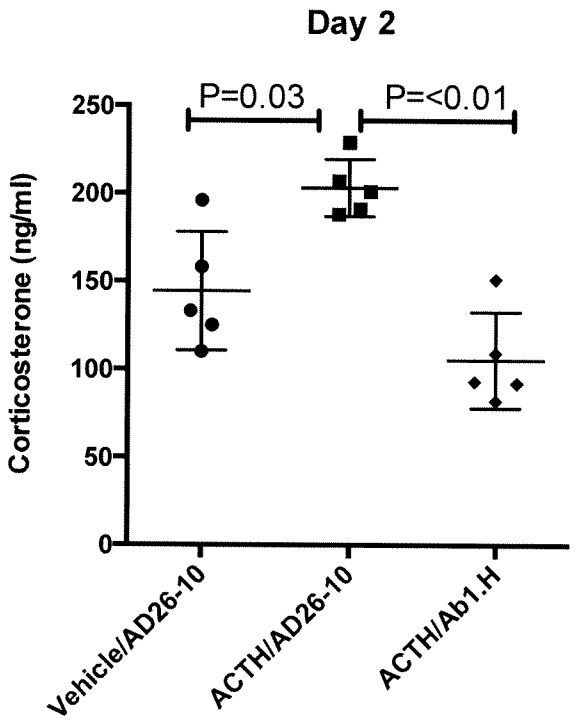


FIG. 46. Plasma corticosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

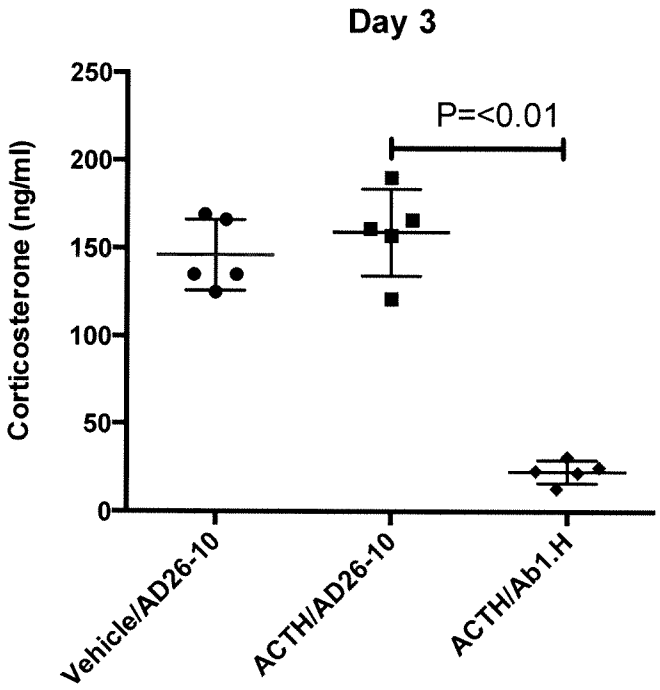


FIG. 47. Plasma corticosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

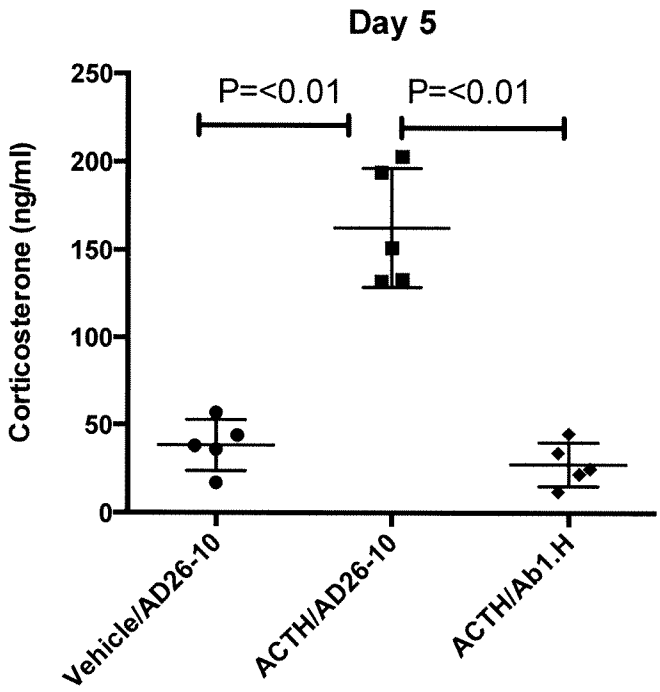


FIG. 48. Plasma corticosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

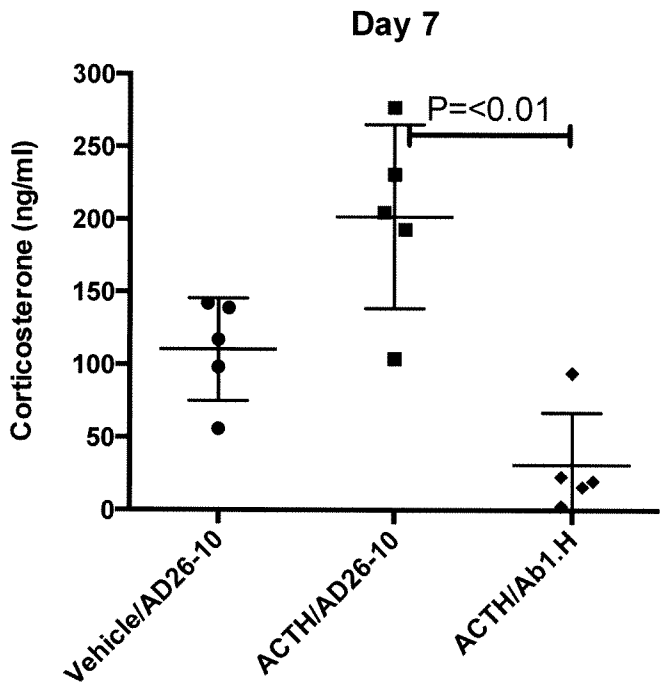


FIG. 49. Plasma corticosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose

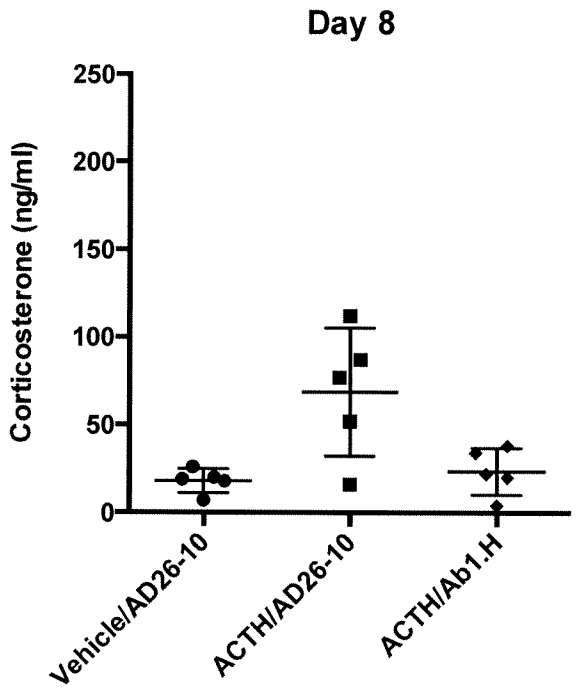


FIG. 50. Plasma corticosterone levels 168 hours post initiation of ACTH dosing and 144 hours post Ab dose

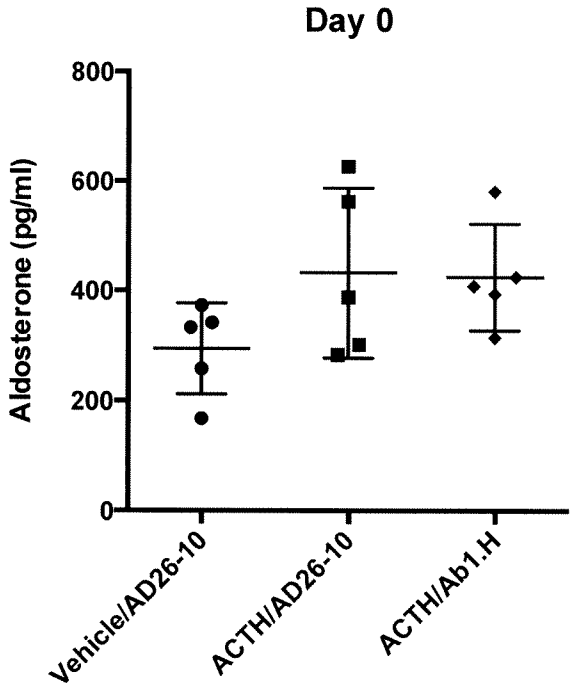


FIG. 51. Plasma aldosterone levels pre-ACTH and Ab dose

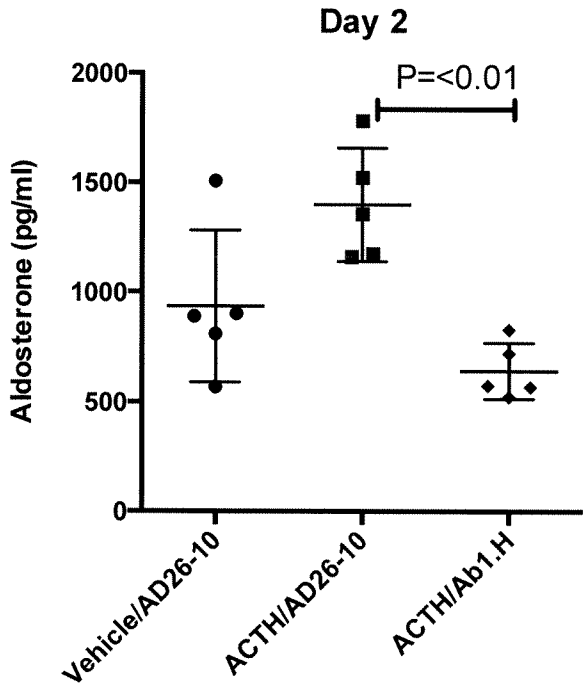


FIG. 52. Plasma aldosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

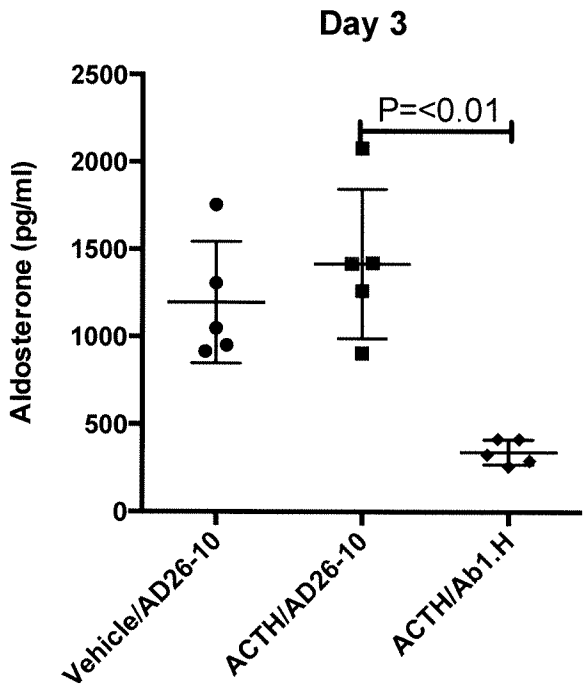


FIG. 53. Plasma aldosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

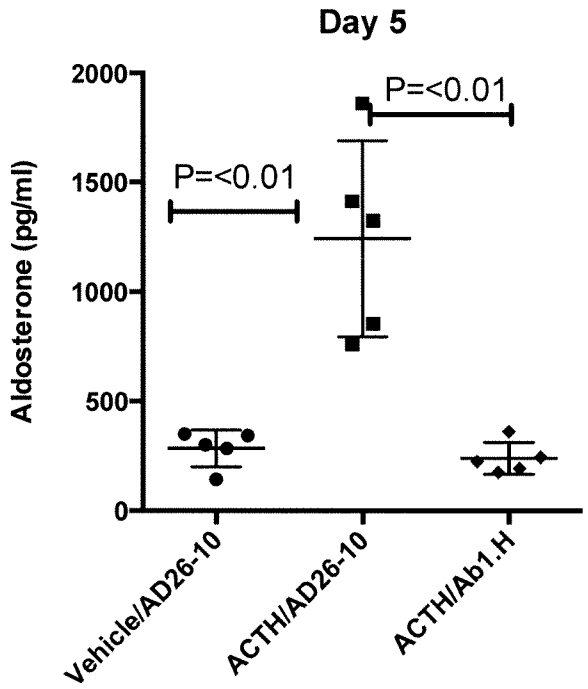


FIG. 54. Plasma aldosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

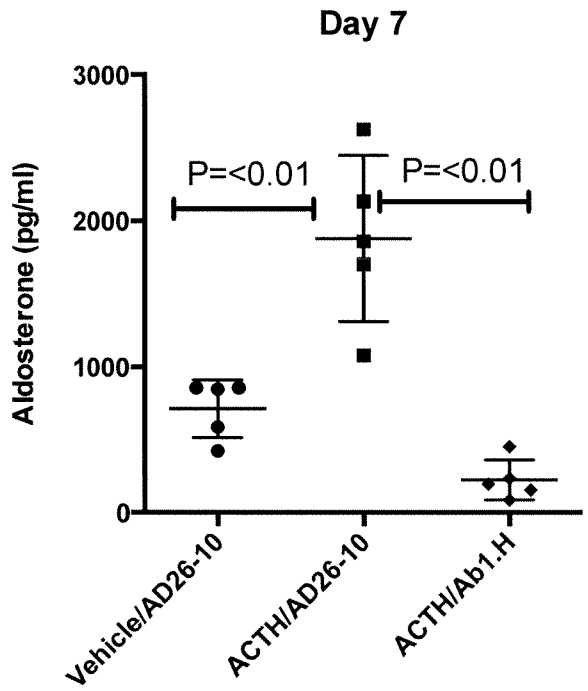


FIG. 55. Plasma aldosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose

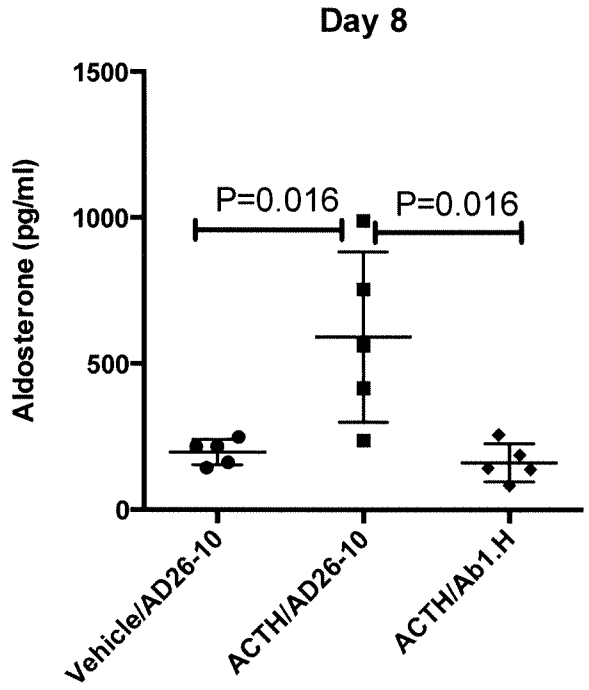
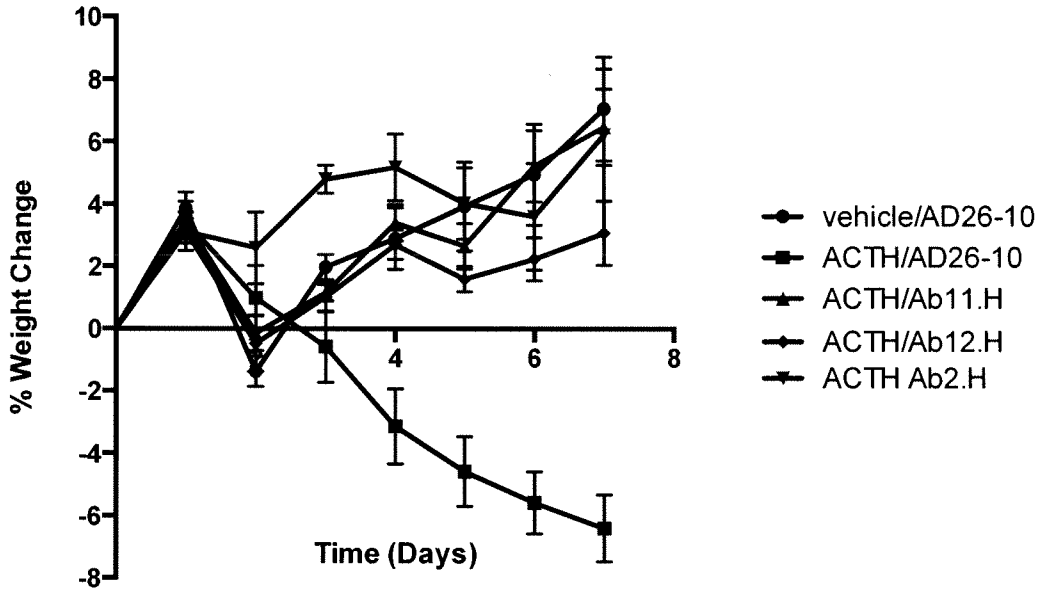


FIG. 56. Plasma aldosterone levels 168 hours post initiation of ACTH dosing and 144 hours post Ab dose



ANOVA Day 7: ACTH/Ab2.H to ACTH/AD26-10 = <0.0001
ANOVA Day 7: ACTH/Ab11.H to ACTH/AD26-10 = <0.0001
ANOVA Day 7: ACTH/Ab12.H to ACTH/AD26-10 = <0.0001

FIG. 57. Ab2.H, Ab11.H, and Ab12.H inhibited ACTH-induced weight loss.

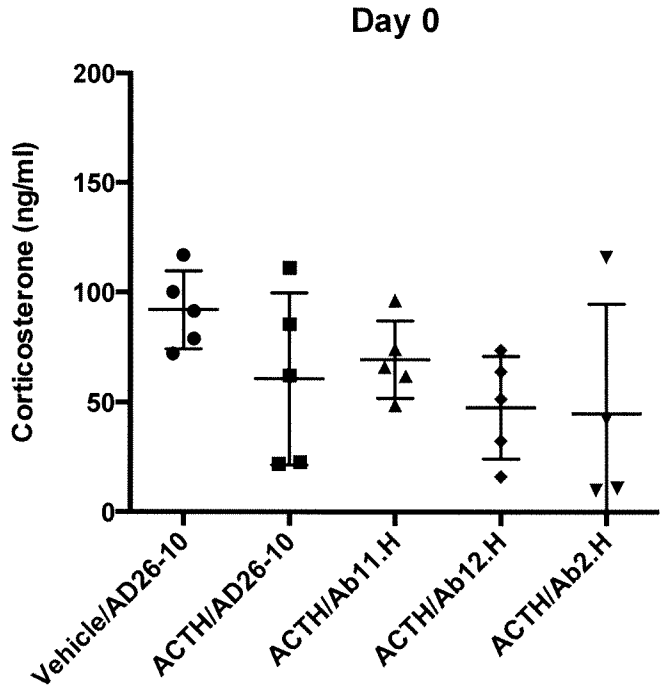


FIG. 58. Plasma corticosterone levels pre-ACTH and Ab dose

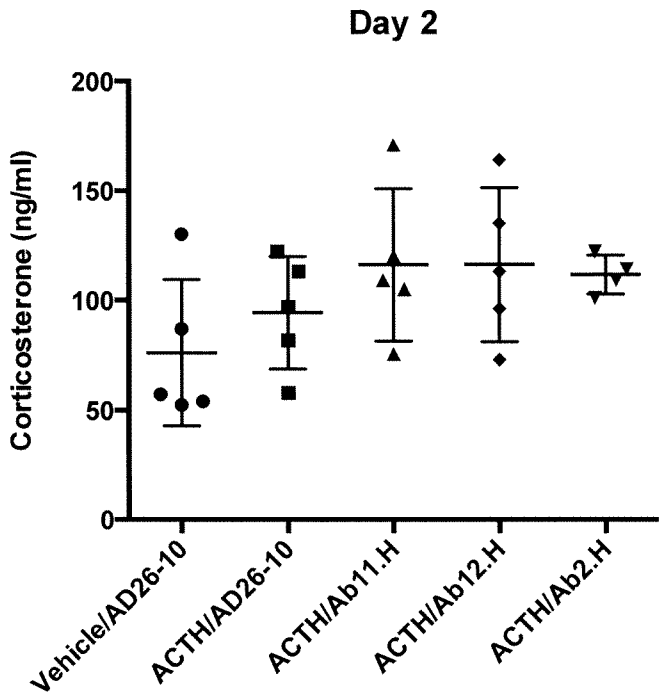


FIG. 59. Plasma corticosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

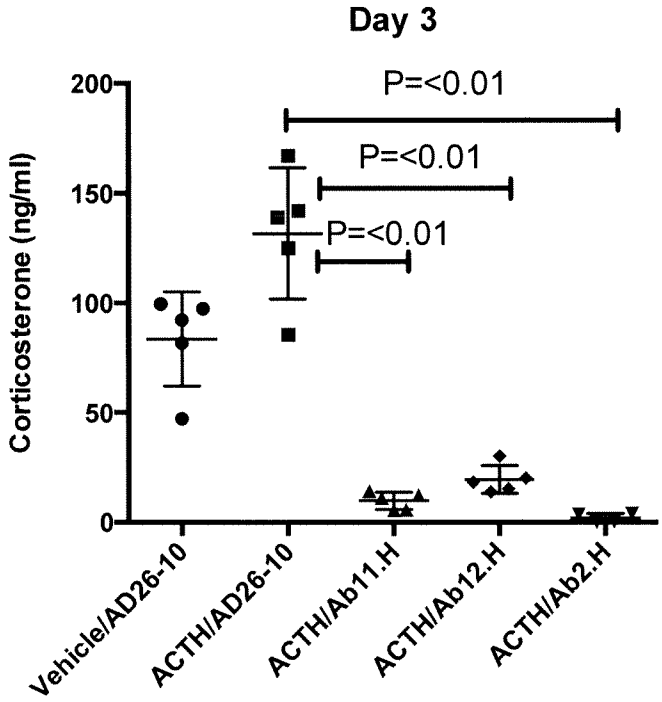


FIG. 60. Plasma corticosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

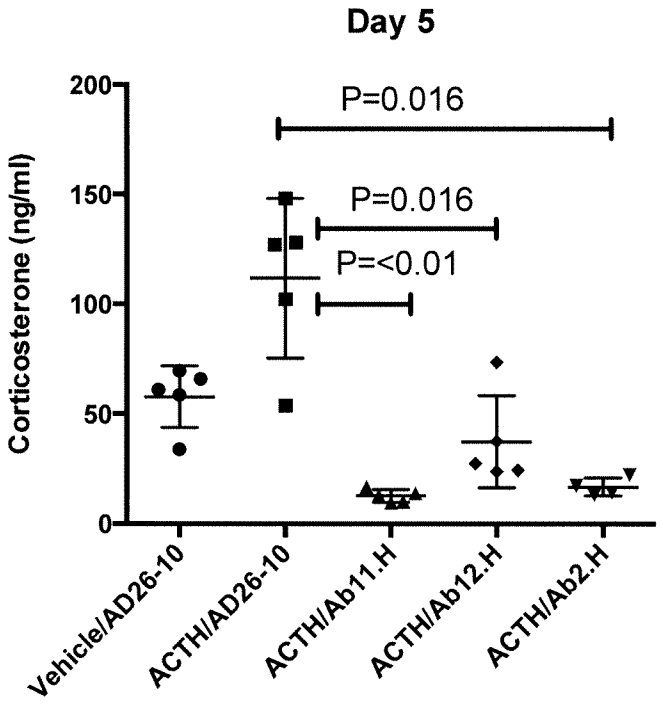


FIG. 61. Plasma corticosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

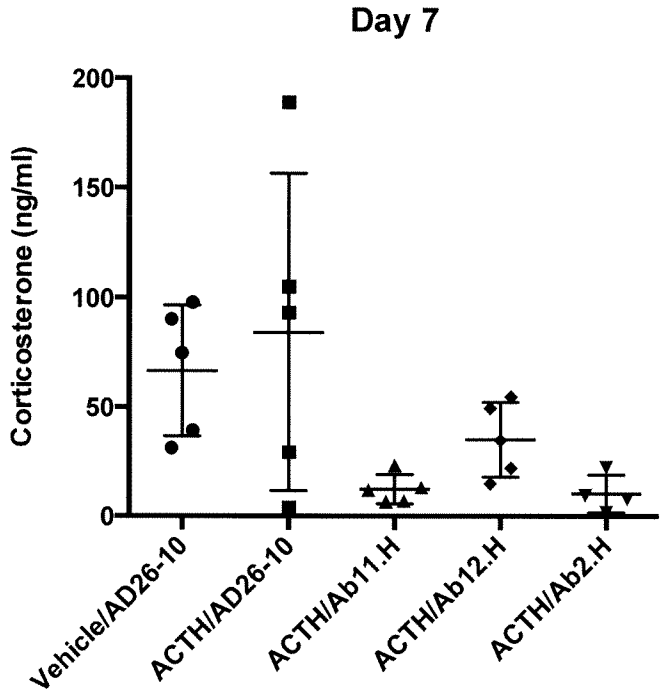


FIG. 62. Plasma corticosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose

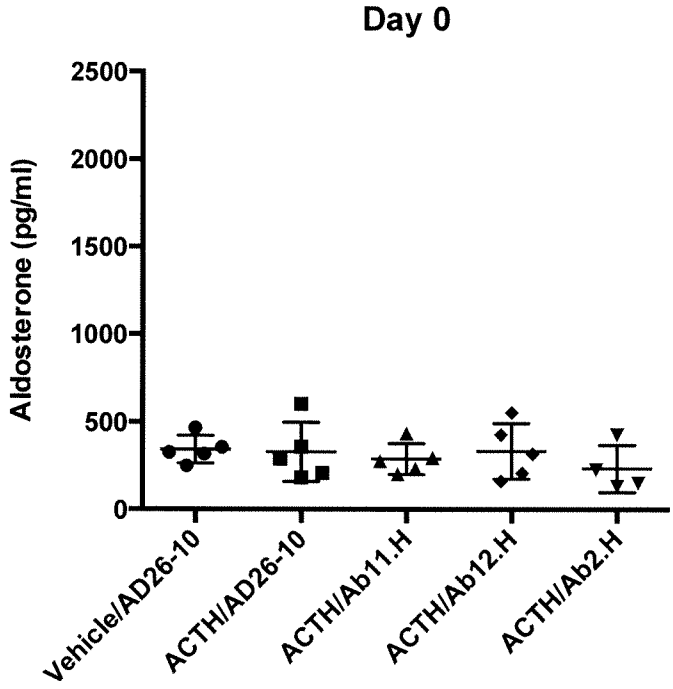


FIG. 63. Plasma aldosterone levels pre-ACTH and Ab dose

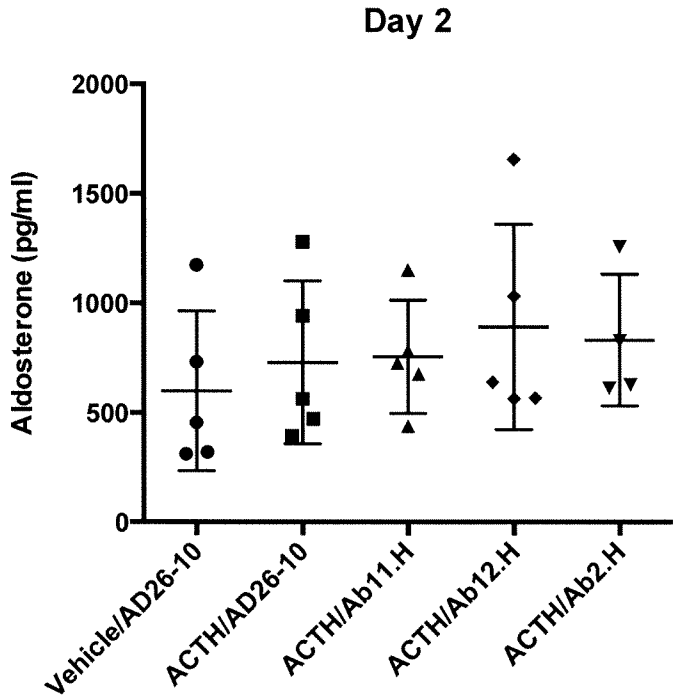


FIG. 64. Plasma aldosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

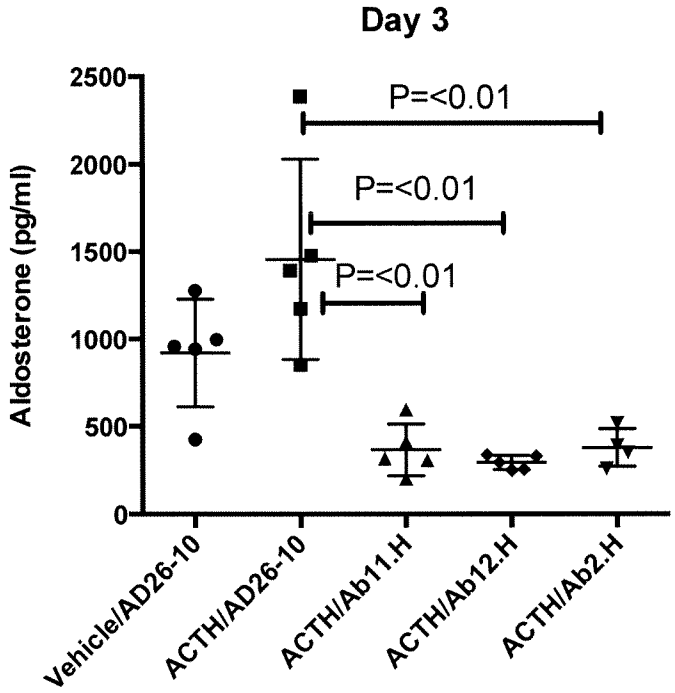


FIG. 65. Plasma aldosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

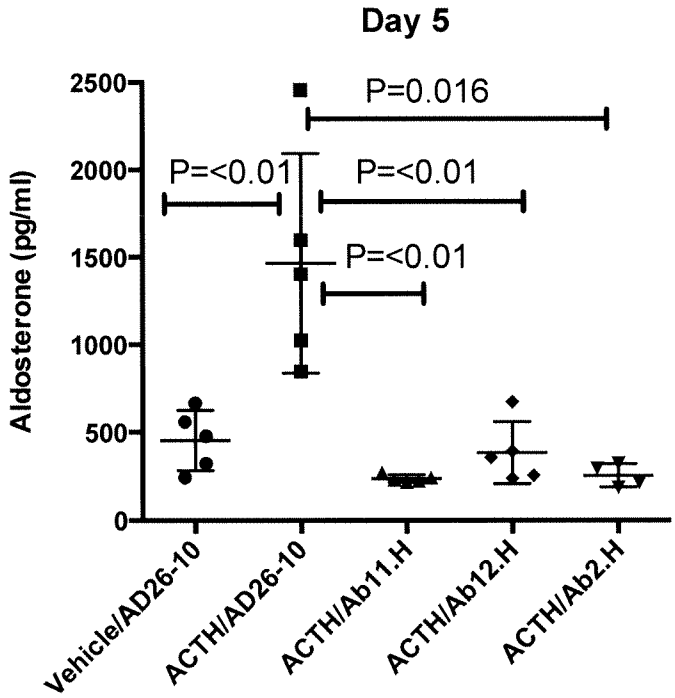


FIG. 66. Plasma aldosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

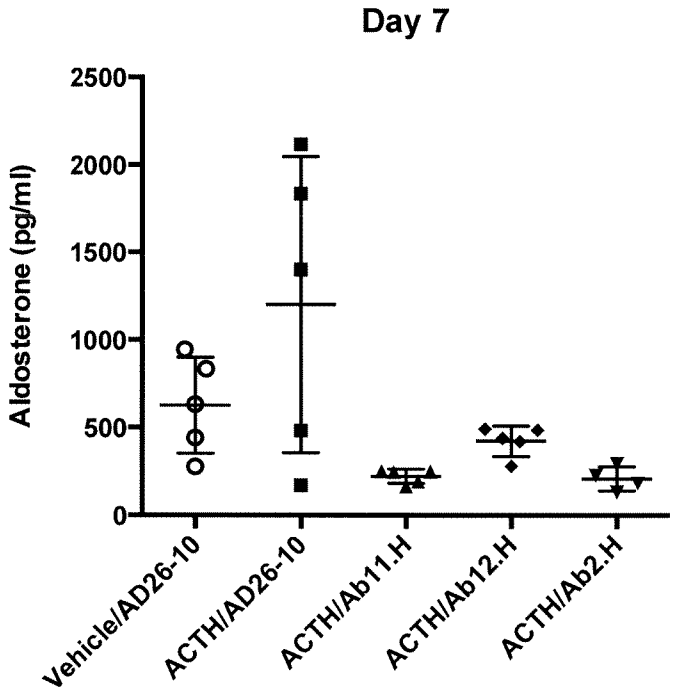
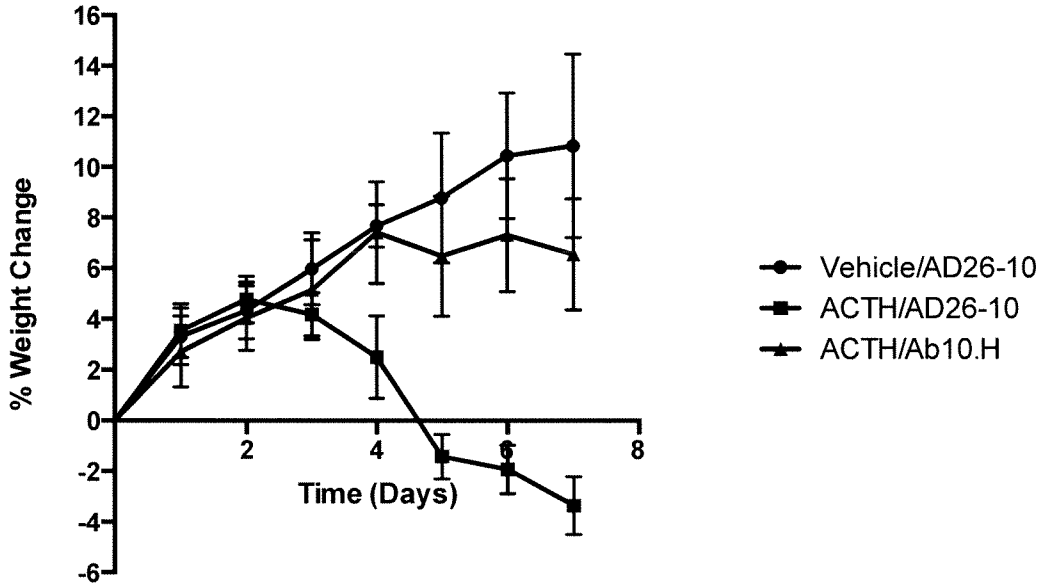


FIG. 67. Plasma aldosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose



ANOVA Day 7: ACTH/Ab10.H to ACTH/AD26-10 = <0.0001

FIG. 68. Ab10.H inhibited ACTH-induced weight loss.

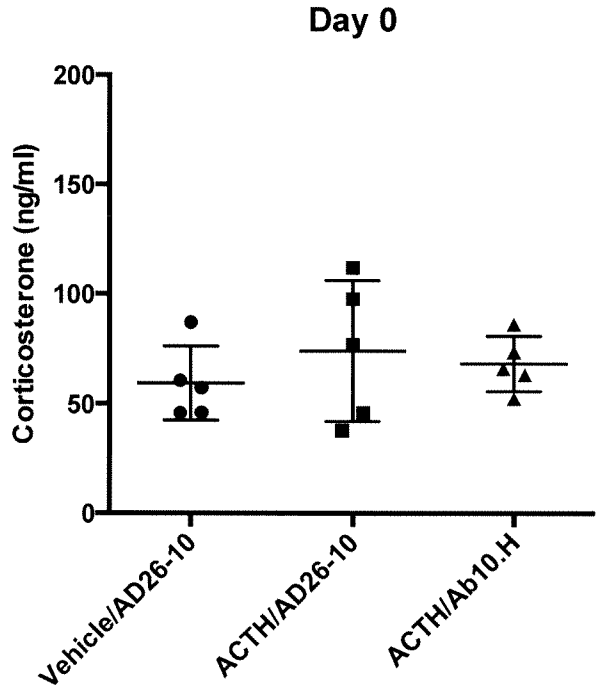


FIG. 69. Plasma corticosterone levels pre-ACTH and Ab dose

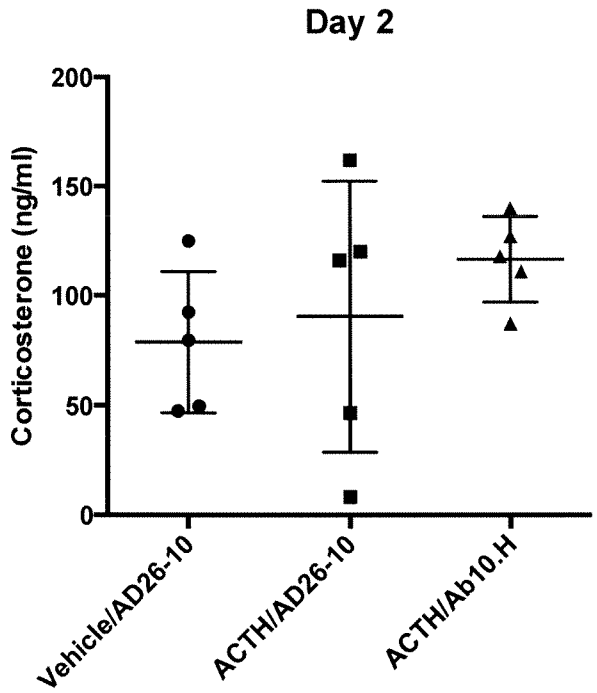


FIG. 70. Plasma corticosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

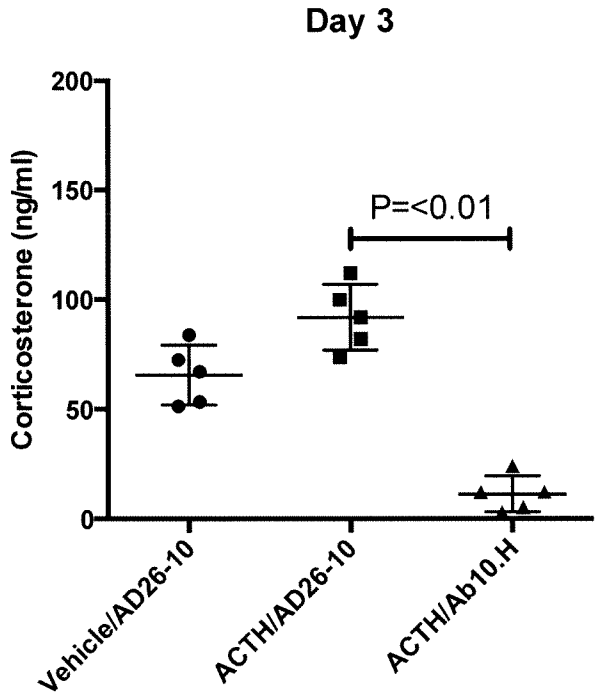


FIG. 71. Plasma corticosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

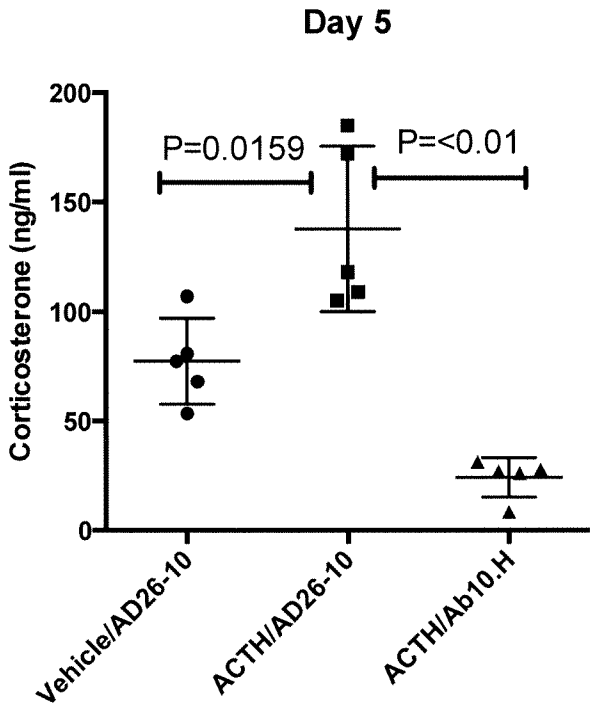


FIG. 72. Plasma corticosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

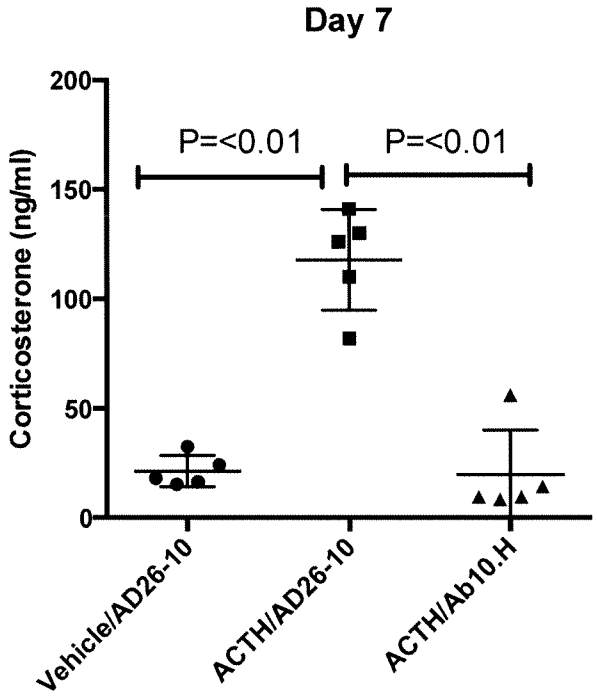


FIG. 73. Plasma corticosterone 144 hours post initiation of ACTH dosing and 120 hours post Ab dose

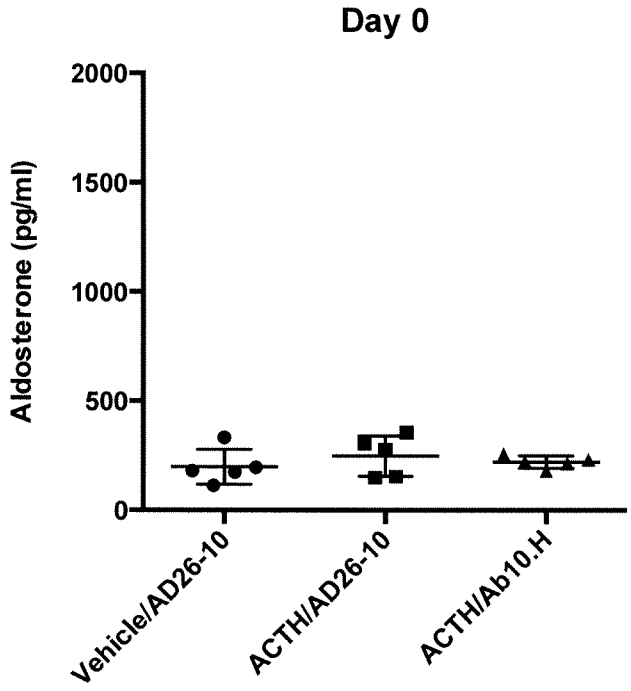


FIG. 74. Plasma aldosterone levels pre-ACTH and Ab dose

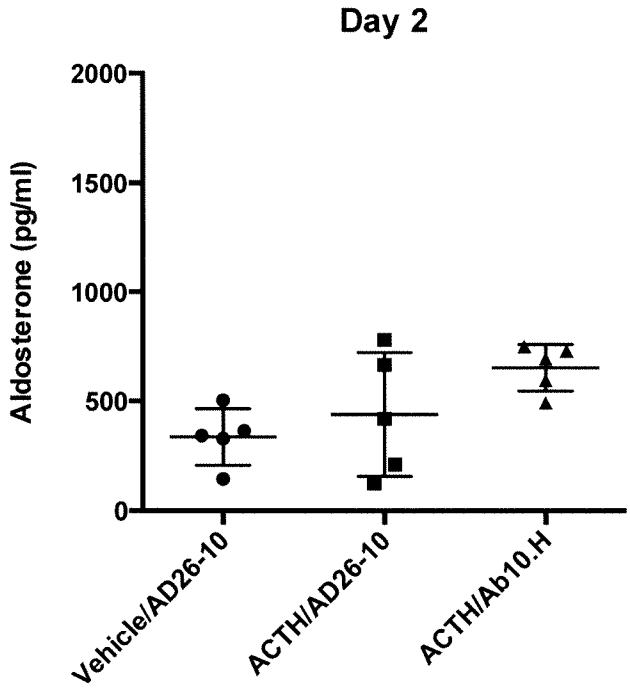


FIG. 75. Plasma aldosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

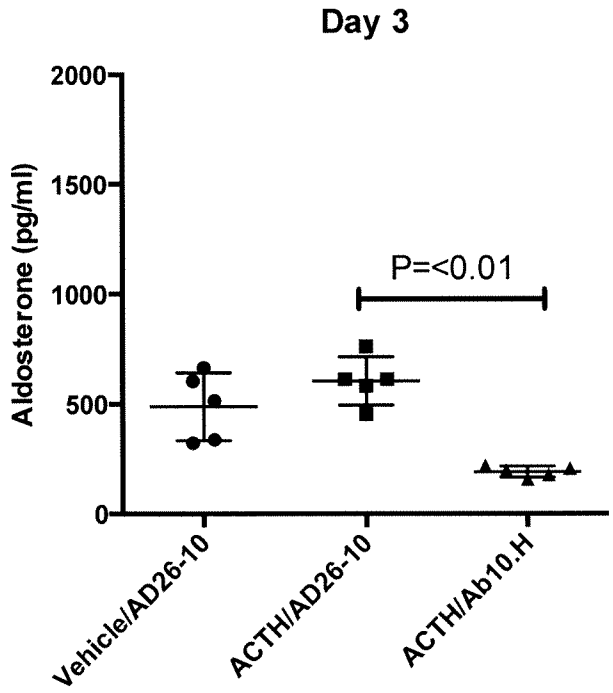


FIG. 76. Plasma aldosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

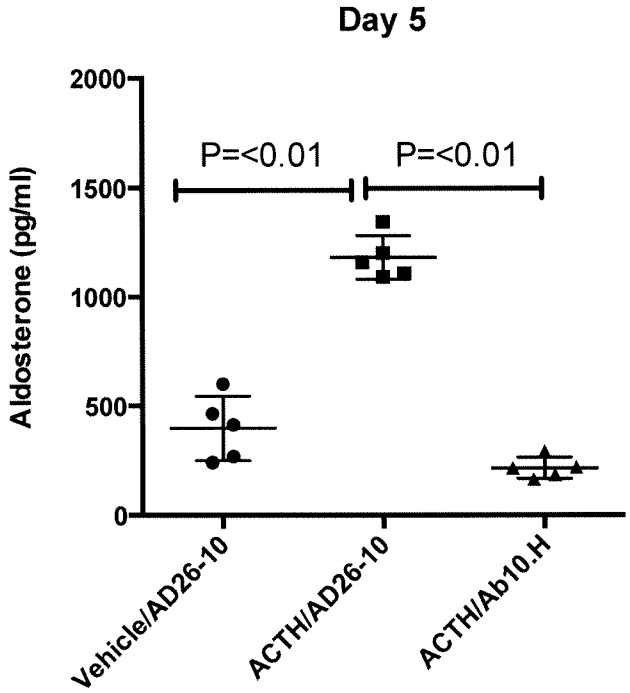


FIG. 77. Plasma aldosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

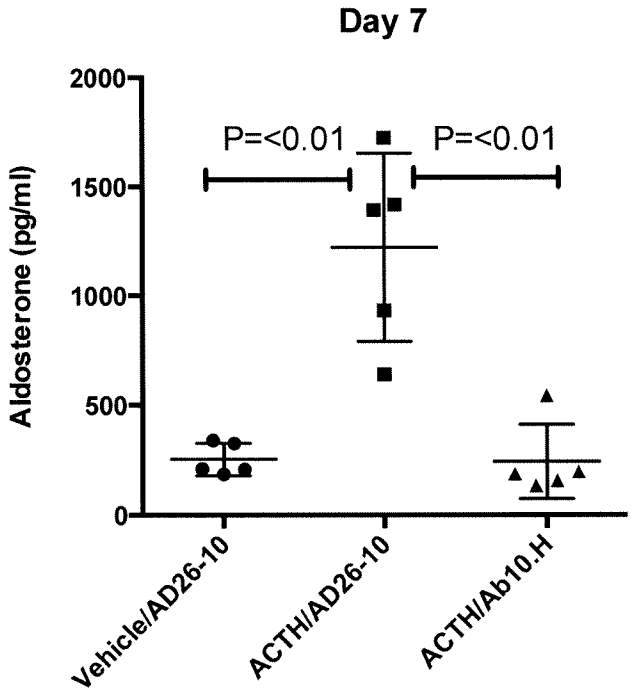
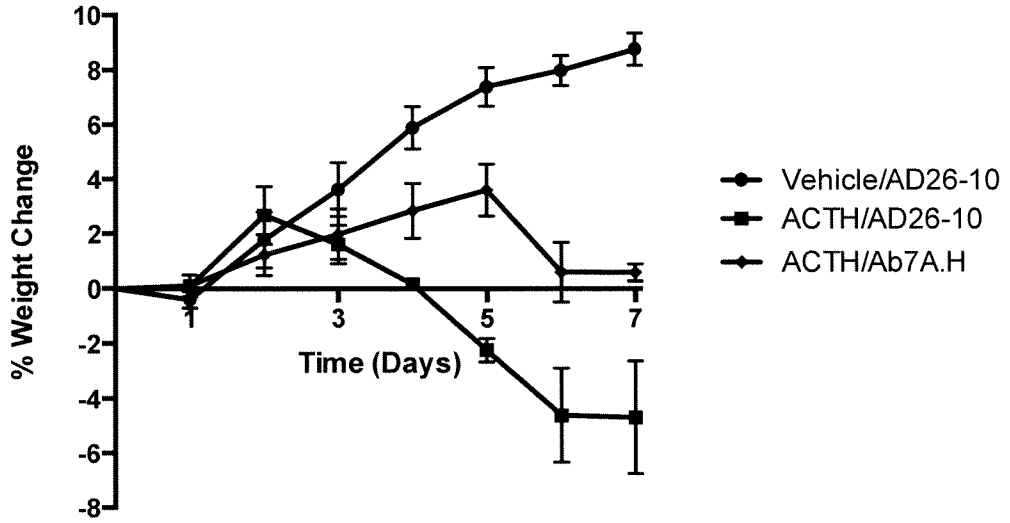


FIG. 78. Plasma aldosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose



ANOVA Day 7: ACTH/Ab7A.H to ACTH/AD26-10 = <0.0001

FIG. 79. Ab7.A.H inhibited ACTH-induced weight loss.

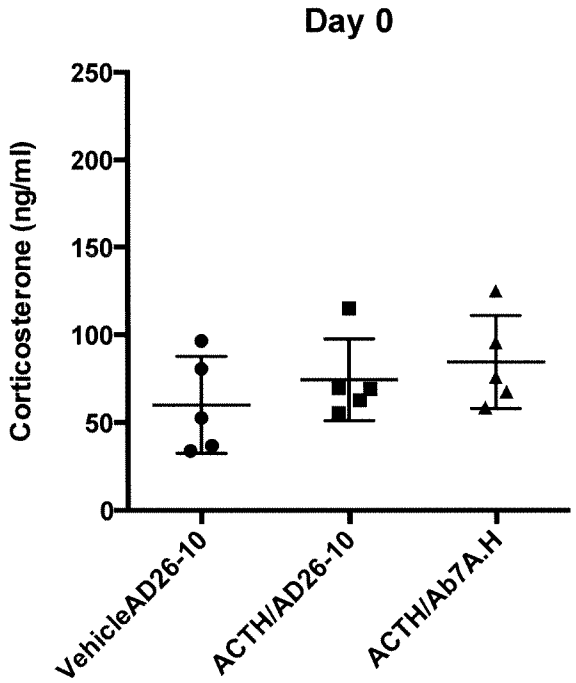


FIG. 80. Plasma corticosterone levels pre-ACTH and Ab dose

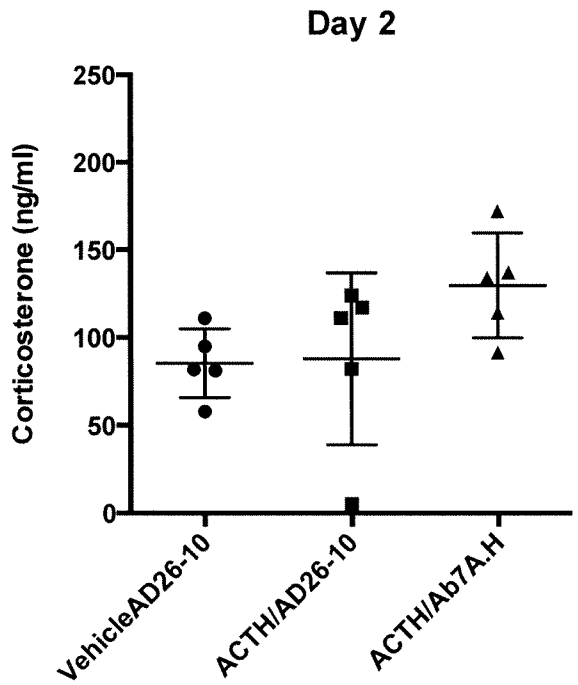


FIG. 81. Plasma corticosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

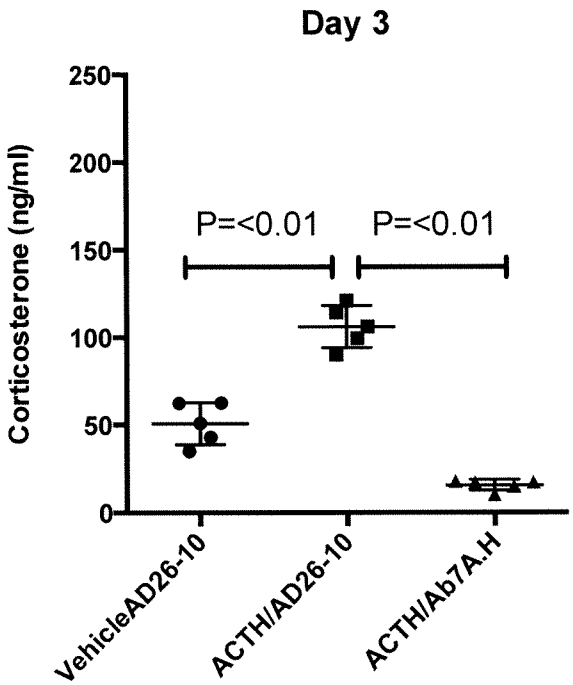


FIG. 82. Plasma corticosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

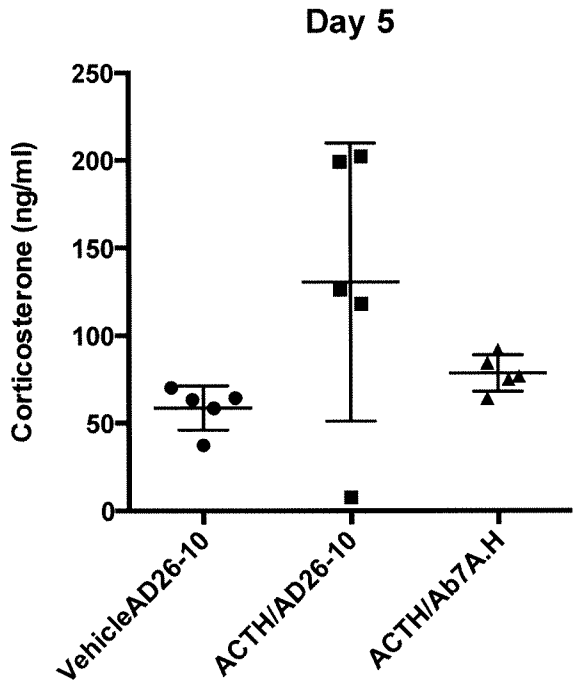


FIG. 83. Plasma corticosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

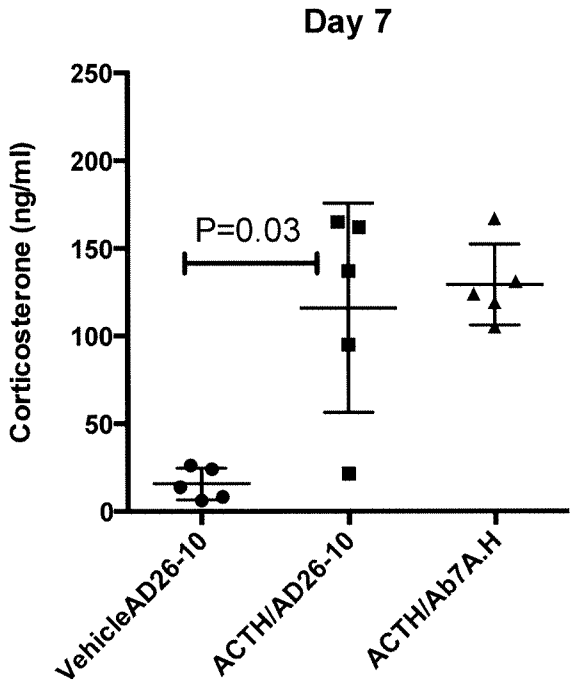


FIG. 84. Plasma corticosterone 144 hours post initiation of ACTH dosing and 120 hours post Ab dose

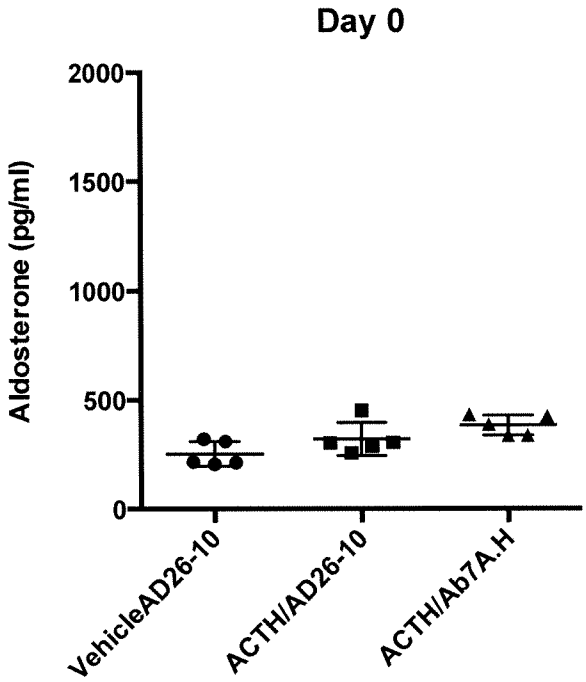


FIG. 85. Plasma aldosterone levels pre-ACTH and Ab dose

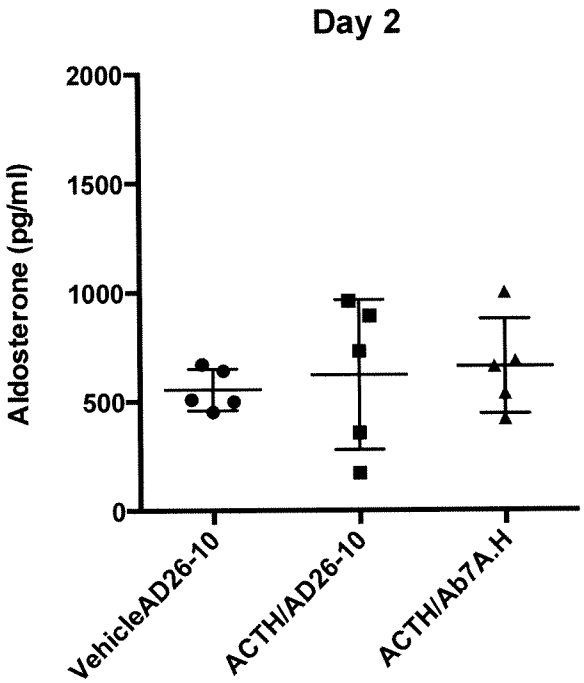


FIG. 86. Plasma aldosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

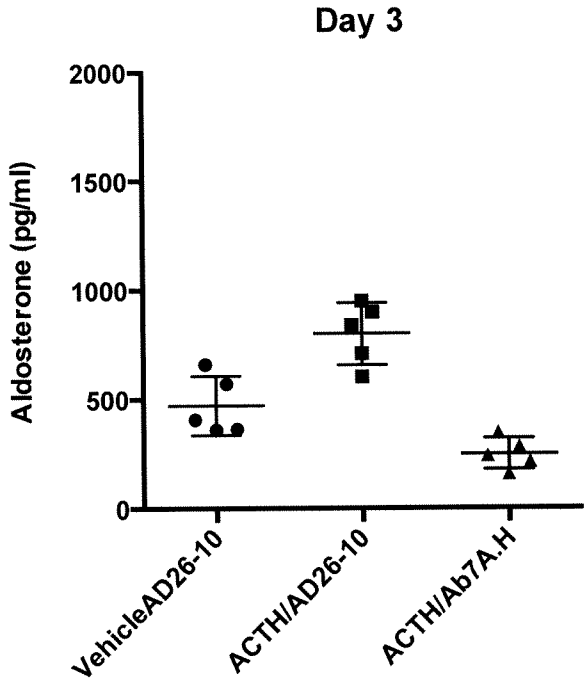


FIG. 87. Plasma aldosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

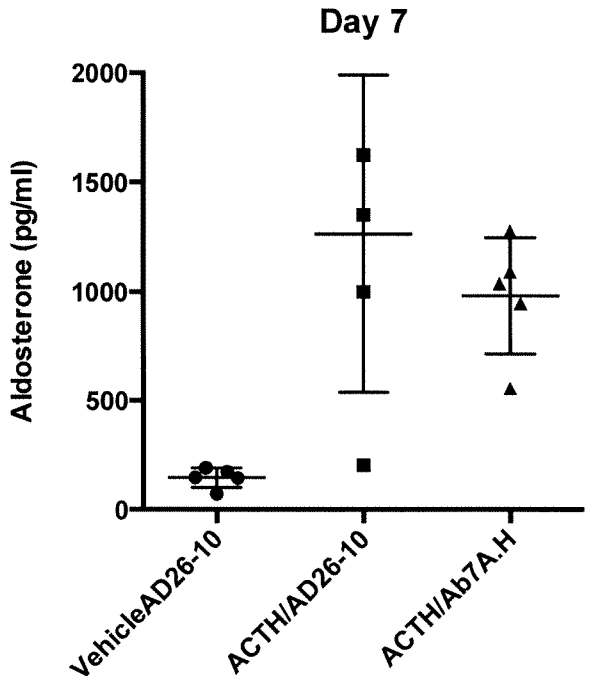


FIG. 89. Plasma aldosterone levels 144 hours post initiation of ACTH dosing and 120 hours post Ab dose

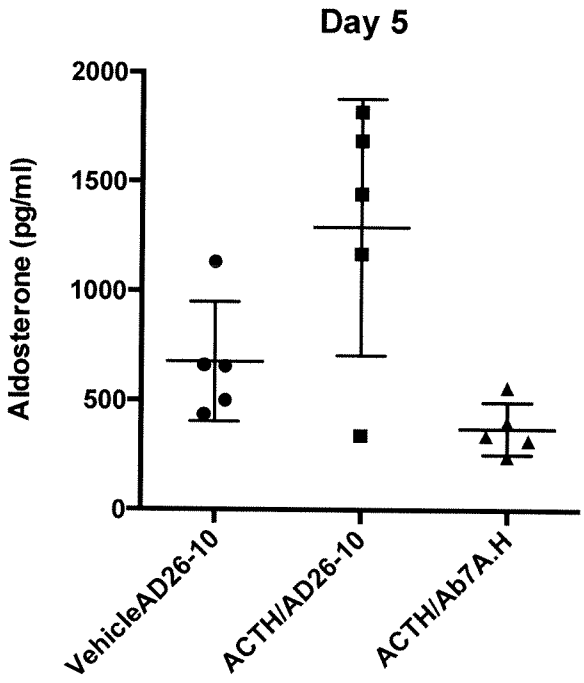


FIG. 88. Plasma aldosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

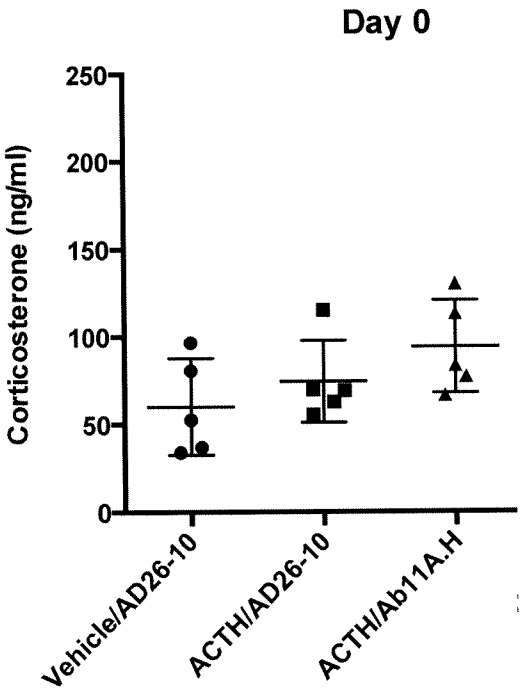


FIG. 90. Plasma corticosterone levels pre-ACTH and Ab dose

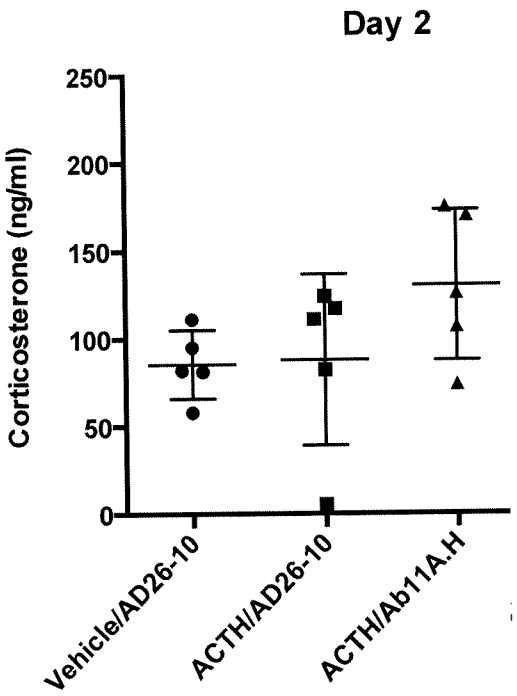


FIG. 91. Plasma corticosterone levels 24 hours post initiation of ACTH dosing and pre-Ab dose

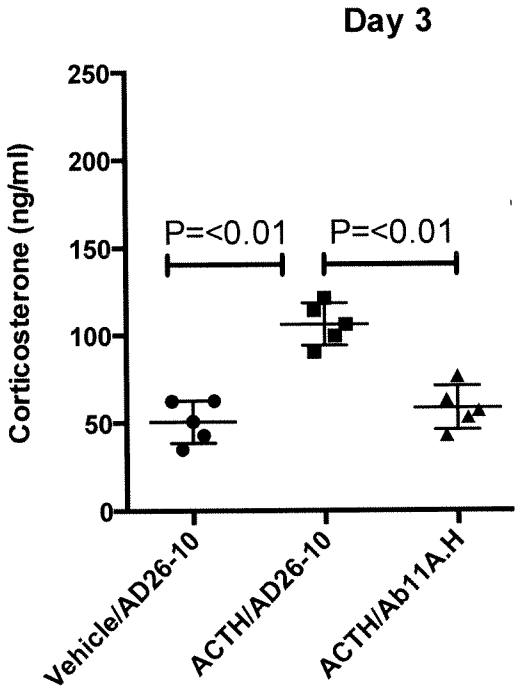


FIG. 92. Plasma corticosterone levels 48 hours post initiation of ACTH dosing and 24 hours post Ab dose

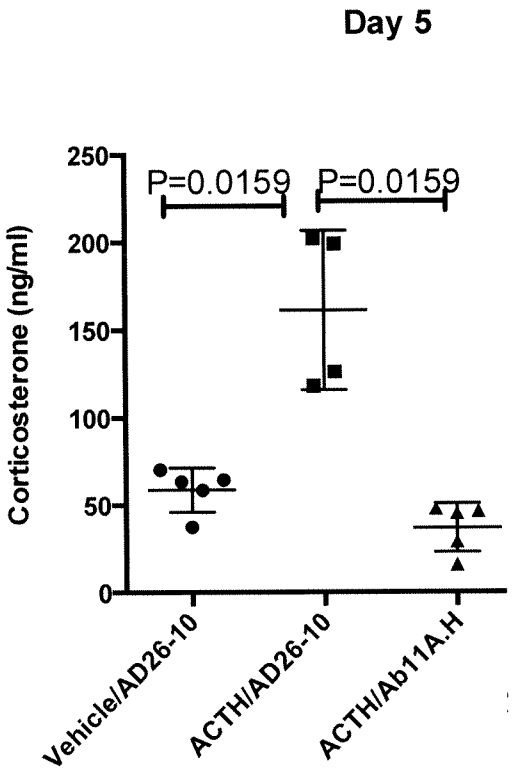


FIG. 93. Plasma corticosterone levels 96 hours post initiation of ACTH dosing and 72 hours post Ab dose

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/16932

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/16932

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8, 10-21
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***-Continued Within the Next Supplemental Box-***-

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/16932

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00; C12P 21/08; C07K 16/00 (2015.00)
CPC - A61K 2039/505; 30/00; C07K 2317/24, 2319/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 39/00; C12P 21/08; C07K 16/00
CPC: A61K 2039/505; 30/00; C07K 2317/24, 2319/00; USPC: 424/178.1, 133.1, 130.1; 530/387.3, 387.1, 386, 380, 350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer; Google; Google Scholar; Dialog ProQuest; Entrez Pubmed; 'anti-ACTH,' 'antibody specificity,' human, humanized, chimeric, epitopes, 'CDRs,' 'heavy chains,' 'light chains'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 2006/0110377 A1 (LIPES, MA et al.) May 25, 2006; paragraphs [0098], [0101]	2-4 ----- 1
Y -- A	US 2013/0302399 A1 (FELDHAUS, AL et al.) November 14, 2013; paragraphs [0006], [0234], [0244], [0253], [0498], [0825]; SEQ ID NOs: 161, 384	4 ----- 1, 5-7, 9
Y --- A	US 2013/0303523 A1 (GOEDERS, ME e tal.) November 14, 2013; paragraphs [0020], [0049]	2, 3 ----- 1, 5-7, 9
A	US 2013/0078216 A1 (DUNLEVY, D et al.) March 28, 2013; paragraphs [0023], [0132]; SEQ ID NO: 59	5-7, 9
A	US 2010/0150918 A1 (KUFER, P et al.) June 17, 2010; paragraphs [0118], [0119], SEQ ID NO: 903	5-7, 9
A	US 2012/0125355 A1 (HIBBERD, JM et al.) May 24, 2012; paragraphs [0238], [0194]; SEQ ID NO: 27	5-7, 9
A	US 2008/0247951 A1 (KOCH, AW et al.) October 9, 2008; paragraph [0029], SEQ ID NO: 46	5-7, 9
A	US 2010/0239582 A1 (HUMPHREYS, DP et al.) September 23, 2010; paragraphs [0088], [0090]; SEQ ID NO: 55	5-7, 9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2015 (15.07.2015)	28 JUL 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US15/16932

-***-Continued from Box No. III: Observations Where Unity of Invention Is Lacking:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1, 4, 5-7 and 9 are directed toward a human, humanized or chimerized anti-human adrenocorticotrophic hormone (ACTH) antibody or antibody fragment encompassing the group consisting of Ab1, Ab2, Ab3, Ab4, Ab5, Ab6, Ab7, Ab9, Ab10, Ab11, Ab12, Ab1.H, Ab2.H, Ab3.H, Ab4.H, Ab6.H, Ab7.H, Ab7A.H, Ab10.H, Ab11.H, Ab11A.H, and Ab12.H.

Group II: Claims 2 and 3 are directed toward a human, humanized or chimerized anti-human adrenocorticotrophic hormone (ACTH) antibody or antibody fragment that specifically binds to an epitope on human ACTH selected from the group consisting of: (i) at least one of residues 16, 18, and 20-23 of human ACTH; (ii) at least one of residues 7-11, 14, and 18 of human ACTH; (iii) at least one of residues 16-18 and 20-23 of human ACTH; (iv) at least one of residues 16-23 of human ACTH, and combinations thereof.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include CDR1, CDR2, and CDR3 polypeptides of SEQ ID NO: 484; SEQ ID NO: 486; and SEQ ID NO: 488, which are not present in Group II, the special technical features of Group II including an anti-human adrenocorticotrophic hormone (ACTH) antibody or antibody fragment that specifically binds to an epitope on human ACTH including at least one of residues 7-11.

Groups I-II share the technical features including anti-ACTH antibodies which specifically bind to at least one of residues 16-18 of human ACTH, and wherein said antibody or fragment does not bind alpha-MSH or CLIP, or binds each of alpha-MSH and CLIP with a Kd (binding affinity) at least 10-fold, at least 100-fold, or at least 1000-fold weaker than the binding affinity of said antibody or fragment for human ACTH.

However, these shared technical features are previously disclosed by the publication entitled 'Epitope Analysis Using Membrane-Immobilized Avidin And Protein A' by Shimazaki, et al. (hereinafter 'Shimazaki').

Shimazaki discloses anti-ACTH antibodies (anti-ACTH antibodies; abstract) which specifically bind to at least one of residues 16-18 of human ACTH (which bind to the WGKPVGK region of ACTH (which specifically bind to at least one of residues 16-18 of human ACTH); abstract), and wherein said antibody or fragment does not bind the amino-terminal 8 residues of ACTH (wherein a polypeptide with the sequence SYSMEHFR was not bound by the antibody; abstract).

Shimazaki does not disclose wherein said antibody or fragment does not bind CLIP, or binds CLIP with a Kd (binding affinity) at least 10-fold, at least 100-fold, or at least 1000-fold weaker than the binding affinity of said antibody or fragment for human ACTH.

It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Shimazaki, for implementing where the antibody does not bind CLIP or binds CLIP with a Kd (binding affinity) at least 10-fold, at least 100-fold, or at least 1000-fold weaker than the binding affinity of said antibody or fragment for human ACTH, based on the fact that the epitope for binding of the antibody, the WGKPVGK region of ACTH, previously disclosed by Shimazaki, is N-terminal to the residues present in CLIP, and a person of ordinary skill in the art would have desired to fully assess the binding determinants for the antibody to the target, and thus would have desired to include the CLIP portion of ACTH, for implementing a lack of antibody binding, or binding with low affinity to this region, provided the previous disclosure of Shimazaki.

Since none of the special technical features of the Groups I-II inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Shimazaki reference, unity of invention is lacking.