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- (73) Patenthaver: **Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591, USA**
- (72) Opfinder: **MACDONALD, Lynn, 16 Gedney Way, White Plains, NY 10605, USA**
MURPHY, Andrew, J., 10 Newton Court, Croton-On-Hudson, NY 10520, USA
CROLL, Susan, D., 176 Bell Hollow Road, Unit 3, Putnam, NY 10579, USA
- (74) Fuldmægtig i Danmark: **Zacco Denmark A/S, Arne Jacobsens Allé 15, 2300 København S, Danmark**
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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind to human glial cell-line derived neurotrophic factor (GDNF) family receptor alpha 3 (GFR α 3), and therapeutic uses of those antibodies.

STATEMENT OF RELATED ART

[0002] The glial cell line-derived neurotrophic factor related family is composed of glial cell line-derived neurotrophic factor (GDNF), neurturin (NRTN), artemin (ARTN) and persephin (PSPN). Each member of the GDNF family binds to a glycosylphosphatidylinositol (GPI)-anchored receptor associated with the plasma membrane. This family of receptors is referred to as the GDNF-family receptor alphas (GFR α s). This receptor family is composed of four different GFR α receptors, GFR α 1-4. GDNF binds preferentially to GFR α 1, NRTN binds preferentially to GFR α 2, ARTN binds preferentially to GFR α 3, and PSPN binds preferentially to GFR α 4. Each GDNF family ligand signals through the RET ("rearranged during transfection") receptor tyrosine kinase, which was first discovered as a proto-oncogene. RET is activated by GDNF family members only if the ligand is first bound to its GFR α receptor (Airaksinen, M.S., et al. Nature Reviews Neuroscience (2002), 3:383-394).

[0003] Both ARTN and GFR α 3 are highly expressed during development and are involved in sympathetic nervous system development. In adult, GFR α 3 expression is largely restricted to the sensory neurons of the dorsal root ganglia (DRG) (Orozco, O.E., et al., European J. Neuroscience, (2001), 13:2177-2182). In adult mouse, artemin is expressed in testis, uterus, thyroid, prostate, and epididymis, as well as in olfactory bulbs and arterioles in the intestine and mesentery (Airaksinen, M.S., et al. Nature Reviews Neuroscience (2002), 3:383-394; Airaksinen, M.S. et al., Brain, Behavior and Evolution, (2006), 68:181-190).

[0004] A possible role for GFR α 3 and artemin in hyperalgesia has been shown in several studies. For example, it has been demonstrated that an injection of the artemin protein into the hindpaw of a rodent caused thermal hyperalgesia and this nociception was enhanced when artemin was co-injected with NGF (Malin, S.A., et al., J. Neuroscience, (2006), 26(33): 8588-8599). Other studies showed that artemin mRNA expression was upregulated in a murine inflammatory model (Elitt, C.M., et al., J. Neuroscience, (2006), 26(33): 8578-8587). Furthermore, other studies showed that artemin transgenic mice have elevated expression of TRPV1 and TRPA1 and have increased behavioral sensitivity to heat and cold (Elitt, C.M., et al., J. Neuroscience, (2006), 26(33): 8578-8587). In addition, a possible role for GFR α 3 in visceral hypersensitivity has been shown by studies in GFR α 3 knockout mice, whereby these mice showed attenuation of visceral hypersensitivity after intracolonic treatment with TNBS (2,4,6-

trinitrobenzene sulfonic acid) relative to wild type C57BL/6 mice (Tanaka, T., et al., Am. J. Physiol. Gastrointest. Liver Physiol. (2011), 300:G418-G424). A possible role for artemin and its receptor GFR α 3 in pain associated with pancreatitis has also been shown by a study done in patients undergoing pancreatic head resection (Ceyhan, G.O., et al., Gut, (2007), 56:534-544). Based on the foregoing, further studies are warranted to determine whether patients suffering from pain/hyperalgesia and/or hypersensitivity could benefit by treatment with an inhibitor of GFR α 3 activity.

[0005] Antibodies that bind GFR α 3 are described in US 6,861,509. In addition, US 6,677,135 discloses a full length GFR α 3 sequence, whereas splice variants of the GFR α 3 molecule are described in US 7,026,138; US2007/0232535 and US2006/0216289. US 7,138,251 discloses sequences that have 99% identity to full length GFR α 3 and the preparation of humanized monoclonal antibodies to this molecule is described in this patent. WO2006/138721 relates to an antibody or antigen-binding fragment thereof that selectively binds to GFR α 3 and inhibits formation of a Neublastin-GFR α 3-Ret ternary complex.

BRIEF SUMMARY OF THE INVENTION

[0006] Described herein are fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that bind to human GFR α 3 and inhibit or block its activity, for example, block the binding of GFR α 3 to the glial cell line-derived neurotrophic factor, artemin, and possibly blocking the subsequent activation of the RET receptor tyrosine kinase and/or blocking signaling through RET and/or blocking signaling through a mediator other than RET. The antibodies or antigen binding fragments thereof may be useful for treating hyperalgesia, allodynia and/or hypersensitivity to any sensory stimulus, including, but not limited to pressure, heat and/or cold. The antibodies may also be used to treat pain/hypersensitivity associated with a wide range of conditions and disorders in which blocking the interaction of GFR α 3 with artemin is desired. The antibodies may also be used to inhibit tumor cell growth, proliferation and/or metastasis.

[0007] In a first aspect, the invention provides an isolated antibody or antigen-binding fragment thereof that binds specifically to human GFR α 3, wherein the antibody comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 381/389 and 397/405.

[0008] In one embodiment, the isolated antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 381/389 and 397/405.

[0009] In one embodiment, the isolated antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NO: 50/58, 146/154, 210/218 and 290/298.

[0010] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof that specifically binds to human GFR α 3 has one or more of the following characteristics:

1. (i) exhibits a K_D ranging from about 10^{-8} M to about 10^{-13} M as measured by surface plasmon resonance;
2. (ii) demonstrates the ability to block about 50-100% of the binding of GFR α 3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 15 nM;
3. (iii) demonstrates the ability to block about 20% to about 100% of the binding of GFR α 3 to a solid support coated with a mixture of artemin and RET;
4. (iv) blocks or inhibits artemin-dependent activation of RET with an IC_{50} ranging from about 200 pM to about 50 nM;
5. (v) inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain;
6. (vi) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo*; or
7. (vii) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis; does not cross-react with other GFR co-receptors for RET(viii)

[0011] In one embodiment, the invention provides an isolated monoclonal antibody or antigen-binding fragment of the invention, wherein:

1. (a) the antibody is selected from the group consisting of a chimeric antibody, a humanized antibody and a human antibody, and/or;
2. (b) the antibody does not cross-react with human GFR α 1 or human GFR α 2, and/or;
3. (c) the antibody is a human monoclonal antibody comprising (a) a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397 and (b) a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0012] In one embodiment, the invention provides an isolated monoclonal antibody or antigen-binding fragment of the invention, wherein:

1. (a) the antibody demonstrates the ability to block about 50-95% of the binding of human GFR α 3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 750

pM;

2. (b) the antibody or the antigen-binding fragment thereof blocks about 75-100% of the binding of human GFR α 3 to its ligand, artemin, with an IC₅₀ value ranging from about 400 pM to about 15 nM;
3. (c) the antibody or the antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of human RET with an IC₅₀ ranging from about 300 pM to about 5 nM; or
4. (d) the antibody or the antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of cynomolgus RET with an IC₅₀ ranging from about 0.7 nM to about 2.5 nM.

[0013] In another aspect, the invention provides an isolated nucleic molecule encoding the antibody or antigen-binding fragment of the invention.

[0014] In another aspect, the invention provides an expression vector comprising the nucleic acid molecule of the invention.

[0015] In another aspect, the invention provides a method of producing an anti-GFR α 3 antibody or antigen-binding fragment thereof comprising the steps of introducing the expression vector of the invention into an isolated host cell, growing the cell under conditions permitting production of the antibody or fragment thereof, and recovering the antibody so produced.

[0016] In another aspect, the invention provides a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of the invention and a pharmaceutically acceptable carrier or diluent.

[0017] In another aspect, the invention provides a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof of the invention and a second therapeutic agent selected from the group consisting of an opioid, a COX-2 inhibitor, a local anesthetic, an NMDA modulator, a cannabinoid receptor agonist, a P2X family modulator, a VR1 antagonist, a substance P antagonist, a second GFR α 3 antagonist, a cytokine or cytokine receptor antagonist, a nerve growth factor (NGF) inhibitor (a small molecular inhibitor or an anti-NGF antibody), an inhibitor of BDNF, TrkA, TrkB or p75, aspirin, a NSAID, a steroid, morphine, a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a tricyclic, an inhibitor of a voltage-gated sodium channel (Na_v), a calcium channel inhibitor, a potassium channel inhibitor, a tumor necrosis factor (TNF) or TNF receptor inhibitor, an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis), a RET inhibitor, an inhibitor of a GDNF family ligand, an inhibitor of GFR α 1, GFR α 2 or GFR α 4, an inhibitor of an acid sensing ion channel (ASIC1 or ASIC3), an anti-convulsant (gabapentin or pregabalin), an inhibitor of a prekineticin receptor (PROK1 and PROK2), a caspase inhibitor, a p38 inhibitor, an IKK1/2 inhibitor, CTLA-4Ig and a corticosteroid; and a pharmaceutically acceptable carrier or diluent;

optionally wherein the second GFR α 3 antagonist is a small organic molecule, a polypeptide antagonist, a second antibody specific for GFR α 3, a siRNA or an antisense molecule specific for GFR α 3; or wherein the cytokine or cytokine receptor antagonist is an interleukin-1 (IL-1) antagonist, an IL-6 antagonist, or an IL-18 antagonist.

[0018] In another aspect, the invention provides the isolated antibody or antigen-binding fragment thereof of the invention, or the pharmaceutical composition of the invention, for use in treating a GFR α 3-related condition or disease, or the pain associated with the GFR α 3-related condition or disease, wherein the GFR α 3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence;

wherein the GFR α 3-related condition or disease is selected from the group consisting of acute pain, chronic pain, neuropathic pain, inflammatory pain, a functional pain syndrome, arthritis, pancreatitis, osteoarthritis, joint pain, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, neurodegenerative disorders, movement disorders, neuroendocrine disorders, ataxia, visceral pain, gout, post-herpetic neuralgia, diabetic neuropathy, sciatica, back pain, head or neck pain, severe or intractable pain, breakthrough pain, post-surgical pain, hereditary erythromelalgia, dental pain, rhinitis, cancer pain, complex regional pain syndrome (CRPS), inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and bladder disorders.

[0019] In one embodiment, the functional pain syndrome is selected from the group consisting of chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome, abdominal pain, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome and Gulf War syndrome; or the cancer pain is associated with a cancer selected from the group consisting of endometrial cancer, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, non-small cell lung cancer, brain cancer, a leukemia, a lymphoma, bone cancer and pain associated with metastasis of a cancer.

[0020] In one embodiment, the antibody, antigen-binding fragment or pharmaceutical composition for use in treating a GFR α 3-related condition or disease, or the pain associated with the GFR α 3-related condition or disease, is for administration to a patient in combination with a second therapeutic agent; wherein said second therapeutic agent is optionally selected from the group consisting of an opioid, a COX-2 inhibitor, a local anesthetic, an NMDA modulator, a cannabinoid receptor agonist, a P2X family modulator, a VR1 antagonist, a substance P antagonist, a second GFR α 3 antagonist, a cytokine or cytokine receptor antagonist, a nerve growth factor (NGF) inhibitor (a small molecular inhibitor or an anti-NGF antibody), an inhibitor of BDNF, TrkA, TrkB or p75, aspirin, a NSAID, a steroid, morphine, a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor

(SNRI), a tricyclic, an inhibitor of a voltage-gated sodium channel (Na_v), a calcium channel inhibitor, a potassium channel inhibitor, a tumor necrosis factor (TNF) or TNF receptor inhibitor, an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis), a RET inhibitor, an inhibitor of a GDNF family ligand, an inhibitor of $\text{GFR}\alpha 1$, $\text{GFR}\alpha 2$ or $\text{GFR}\alpha 4$, an inhibitor of an acid sensing ion channel (ASIC1 or ASIC3), an anti-convulsant (gabapentin or pregabalin), an inhibitor of a prekineticin receptor (PROK1 and PROK2), a caspase inhibitor, a p38 inhibitor, an IKK1/2 inhibitor, CTLA-4Ig and a corticosteroid; and a pharmaceutically acceptable carrier or diluent; optionally wherein the second $\text{GFR}\alpha 3$ antagonist is a small organic molecule, a polypeptide antagonist, a second antibody specific for $\text{GFR}\alpha 3$, a siRNA or an antisense molecule specific for $\text{GFR}\alpha 3$; or wherein the cytokine or cytokine receptor antagonist is an interleukin-1 (IL-1) antagonist, an IL-6 antagonist, or an IL-18 antagonist.

[0021] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof is selected from the group consisting of a murine, chimeric, humanized and a human antibody.

[0022] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof does not cross-react with human $\text{GFR}\alpha 1$ or human $\text{GFR}\alpha 2$.

[0023] An isolated monoclonal antibody or an antigen-binding fragment thereof described herein may comprise (a) a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397 and (b) a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0024] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof demonstrates the ability to block about 50-95% of the binding of human $\text{GFR}\alpha 3$ to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 750 pM.

[0025] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof blocks about 75-100% of the binding of human $\text{GFR}\alpha 3$ to its ligand, artemin, with an IC_{50} value ranging from about 400 pM to about 15 nM.

[0026] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of human RET with an IC_{50} ranging from about 300 pM to about 5 nM.

[0027] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof blocks or inhibits artemin-dependent activation of cynomolgus RET with an IC_{50} ranging from about 0.7 nM to about 2.5 nM.

[0028] An isolated monoclonal antibody or an antigen-binding fragment thereof described

herein may comprise the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0029] An isolated monoclonal antibody or an antigen-binding fragment thereof described herein may comprise a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397.

[0030] An isolated monoclonal antibody or an antigen-binding fragment thereof described herein may comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405.

[0031] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 381/389 and 397/405.

[0032] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NO: 50/58, 146/154, 210/218 and 290/298.

[0033] An isolated monoclonal antibody or an antigen-binding fragment thereof described herein may comprise:

1. (a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 383 and 399;
2. (b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 385 and 401;
3. (c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 387 and 403;
4. (d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 391 and 407;
5. (e) a LCDR2 domain having an amino acid sequence selected from the group consisting

of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 393 and 409; and

6. (f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 395 and 411.

[0034] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof competes for specific binding to human GFR α 3 with an antibody or antigen-binding fragment comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362, 381/389 and 397/405.

[0035] In one embodiment, the isolated monoclonal antibody or an antigen-binding fragment thereof binds the same epitope on human GFR α 3 that is recognized by an antibody comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346 and 354/362, 381/389 and 397/405.

[0036] The antibodies of the invention can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, F(ab')₂ or scFv fragment), and may be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933).

[0037] An isolated antibody or antigen-binding fragment thereof that binds specifically to human GFR α 3 described herein may comprise a HCVR comprising the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within the HCVR amino acid sequences selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; and/or a LCVR comprising the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the LCVR amino acid sequences selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. See, e.g., Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani et al., J. Mol. Biol. 273:927-948 (1997); and Martin et al., Proc. Natl. Acad.

Sci. USA 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0038] An isolated antibody or antigen-binding fragment that specifically binds human GFR α 3 described herein may comprise:

1. (a) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 387 and 403; and
2. (b) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 395 and 411.

[0039] An isolated antibody or antigen-binding fragment that specifically binds human GFR α 3, as described in (a) and (b) above, may further comprise:

(c) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 383 and 399;

(d) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 385 and 401;

(e) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 391 and 407; and

(f) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 393 and 409.

[0040] Further described herein is a fully human monoclonal antibody or antigen-binding fragment thereof that binds specifically to human GFR α 3, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 387 and 403, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at

least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 395 and 411 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 383 and 399 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 385 and 401 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 391 and 407 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 393 and 409 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) exhibits a K_D ranging from about 10^{-8} M to about 10^{-13} M as measured by surface plasmon resonance; (vi) demonstrates the ability to block about 50-100% of the binding of GFR α 3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 15 nM; (vii) demonstrates the ability to block about 20% to about 100% of the binding of GFR α 3 to a solid support coated with a mixture of artemin and RET; (viii) blocks or inhibits artemin-dependent activation of RET with an IC_{50} ranging from about 200 pM to about 50 nM; (ix) inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain; (x) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo*; (xi) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis; (xii) does not cross-react with other GFR co-receptors for RET.

[0041] Described herein is an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain having an amino acid sequence selected from any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0042] Described herein is an antibody or fragment thereof further comprising a HCDR1 domain having an amino acid sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence of any of those shown on Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence of

any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0043] In certain embodiments, the antibody or antigen-binding portion of an antibody that specifically binds to human GFR α 3 comprises a HCDR3/LCDR3 amino acid sequence pair selected from any of the HCDR3/LCDR3 amino acid sequences shown in Table 1. According to certain embodiments, the antibody or antigen-binding portion of an antibody comprises a HCDR3/LCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NOs: 8/16, 24/32, 40/48, 56/64, 72/80, 88/96, 104/112, 120/128, 136/144, 152/160, 168/176, 184/192, 200/208, 216/224, 232/240, 248/256, 264/272, 280/288, 296/304, 312/320, 328/336, 344/352, 360/368, 387/395 and 403/411.

[0044] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 4, 6 and 8, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 12, 14 and 16, respectively.

[0045] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 20, 22 and 24, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 28, 30 and 32, respectively.

[0046] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 36, 38 and 40, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 44, 46 and 48, respectively.

[0047] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 52, 54 and 56, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 60, 62 and 64, respectively.

[0048] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 68, 70 and 72, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 76, 78 and 80, respectively.

[0049] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 84, 86 and 88, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 92, 94 and 96, respectively.

[0050] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 100, 102 and 104, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 108, 110 and 112, respectively.

[0051] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 116, 118 and 120, respectively and

LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 124, 126 and 128, respectively.

[0052] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 132, 134 and 136, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 140, 142 and 144, respectively.

[0053] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 148, 150 and 152, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 156, 158 and 160, respectively.

[0054] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 164, 166 and 168, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 172, 174 and 176, respectively.

[0055] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 180, 182 and 184, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 188, 190 and 192, respectively.

[0056] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 196, 198 and 200, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 204, 206 and 208, respectively.

[0057] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 212, 214 and 216, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 220, 222 and 224, respectively.

[0058] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 228, 230 and 232, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 236, 238 and 240, respectively.

[0059] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 244, 246 and 248, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 252, 254 and 256, respectively.

[0060] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 260, 262 and 264, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 268, 270 and 272, respectively.

[0061] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 276, 278 and 280, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 284, 286 and 288, respectively.

[0062] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 292, 294 and 296, respectively and

LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 300, 302 and 304, respectively.

[0063] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 308, 310 and 312, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 316, 318 and 320, respectively.

[0064] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 324, 326 and 328, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 332, 334 and 336, respectively.

[0065] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 340, 342 and 344, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 348, 350 and 352, respectively.

[0066] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 356, 358 and 360, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 364, 366 and 368, respectively.

[0067] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 383, 385 and 387, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 391, 393 and 395, respectively.

[0068] In one embodiment, the antibody or antigen binding fragment thereof comprises the HCDR1, HCDR2 and HCDR3 sequences of SEQ ID NOs: 399, 401 and 403, respectively and LCDR1, LCDR2 and LCDR3 sequences of SEQ ID NOs: 407, 409 and 411, respectively.

[0069] Certain non-limiting, exemplary antibodies and antigen-binding fragments described herein comprise HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 domains, respectively, selected from any of the amino acid sequences shown in Table 1.

[0070] In another aspect, the invention provides nucleic acid molecules encoding anti-GFR α 3 antibodies or fragments thereof of the invention. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0071] In one embodiment, the invention provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, 337, 353, 380 and 396 or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 49, 145, 209 and 289.

[0072] In one embodiment, the antibody or fragment thereof further comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, 345, 361, 388 and 404 or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. In one embodiment, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 57, 153, 217 and 297.

[0073] Also described herein is an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence located within the variable regions from any of the antibodies shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain encoded by a nucleotide sequence selected from any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0074] Also described herein is an antibody or fragment thereof further comprising a HCDR1 domain encoded by a nucleotide sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain encoded by a nucleotide sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain encoded by a nucleotide sequence of any of those shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain encoded by a nucleotide sequence shown in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0075] Further described herein is a human anti-hGFR α 3 antibody or antigen-binding fragment of an antibody comprising a HCVR encoded by nucleotide sequence segments derived from V_H, D_H and J_H germline sequences, and a LCVR encoded by nucleotide sequence segments derived from V_K and J_K germline sequences, with combinations as shown in Table 2.

[0076] The invention encompasses anti-hGFR α 3 antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0077] In another aspect, the invention features a pharmaceutical composition comprising a recombinant human antibody or fragment thereof of the invention, which specifically binds hGFR α 3 and a pharmaceutically acceptable carrier. In one embodiment, the invention features a composition, which is a combination of an antibody or antigen-binding fragment of an antibody of the invention, and a second therapeutic agent. The second therapeutic agent may

be any agent that is advantageously combined with the antibody or fragment thereof of the invention, for example, an agent capable of reducing pain, such as, but not limited to, opioids, morphine, a COX-2 inhibitor, aspirin, or other non-steroidal anti-inflammatories, acetaminophen, duloxetine, local anesthetics, NMDA modulators, cannabinoid receptor agonists, P2X family modulators, VR1 antagonists, and substance P antagonists. The second therapeutic agent may be an interleukin-1 (IL-1) inhibitor, for example, a fusion protein (US 6,927,044); or an antiepileptic/anticonvulsant drug, such as gabapentin, pregabalin, topiramate; or a tricyclic antidepressant, such as amitriptyline; a cytokine inhibitor or antagonist, such as an antagonist to IL-6, IL-6R, IL-18 or IL-18R, or an inhibitor of a voltage-gated sodium channel, such as a $\text{Na}_v1.7$ inhibitor, or a $\text{Na}_v1.8$ inhibitor, or a $\text{Na}_v1.9$ inhibitor; an inhibitor of a potassium channel or calcium channel; or a NGF inhibitor (a small molecule inhibitor or an anti-NGF antibody), or a second inhibitor or antagonist to GFR α 3, a tumor necrosis factor (TNF) or TNF receptor inhibitor, an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis), a RET inhibitor, an inhibitor of a GDNF family ligand, an inhibitor of GFR α 1, GFR α 2 or GFR α 4, an inhibitor of an acid sensing ion channel (e.g. ASIC1 or ASIC3), or a selective serotonin reuptake inhibitor (SSRI), or a serotonin norepinephrine reuptake inhibitor (SNRI), or an inhibitor of a prekineticin receptor (e.g. PROK1 and PROK2), or a caspase inhibitor, a p38 inhibitor, an IKK1/2 inhibitor, CTLA-4Ig, or a corticosteroid. The second therapeutic agent may be a small molecule drug or a protein/polypeptide inhibitor. The second therapeutic agent may be synthetic or naturally derived. The second therapeutic agent may be a second antibody specific for GFR α 3, a polypeptide antagonist, a siRNA or an antisense molecule specific for GFR α 3. It will also be appreciated that the antibodies and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the antibodies and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an antibody may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are appropriate for the disease, or condition, being treated.

[0078] Further described herein are methods for inhibiting hGFR α 3 activity using an anti-hGFR α 3 antibody or antigen-binding portion of an antibody of the invention, wherein the methods comprise administering a therapeutically effective amount of one or more antibodies of the invention, or antigen binding fragments thereof, or a pharmaceutical composition comprising one or more antibodies of the invention or antigen-binding fragments thereof.

[0079] A method for treating a GFR α 3-related condition or disease, or the pain associated with a GFR α 3-related condition or disease is also described herein, the method comprising administering an anti-GFR α 3 antibody or antigen-binding portion of an antibody of the invention, or a composition comprising an anti-GFR α 3 antibody or a fragment thereof, to a

patient in need thereof, wherein the GFR α 3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

[0080] In one embodiment, the invention provides for the isolated antibody of the invention or antigen-binding fragment thereof, or a pharmaceutical composition comprising at least one antibody or antigen-binding fragment thereof of the invention for use in treating a GFR α 3-related condition or disease, or the pain associated with the GFR α 3-related condition or disease, wherein the GFR α 3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

[0081] Use of an isolated antibody or antigen-binding fragment thereof of the invention, or a pharmaceutical composition comprising at least one antibody of the invention in the manufacture of a medicament for treating a GFR α 3-related condition or disease, or the pain associated with the GFR α 3-related condition or disease, is described herein, wherein the GFR α 3-related condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence, or the pain associated with the condition or disease is prevented, ameliorated, or reduced in severity or frequency of occurrence.

[0082] In one embodiment, the GFR α 3-related condition or disease is selected from the group consisting of acute pain, chronic pain, neuropathic pain, inflammatory pain, a functional pain syndrome, arthritis, pancreatitis, osteoarthritis, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, neurodegenerative disorders, movement disorders, neuroendocrine disorders, ataxia, visceral pain, acute gout, post-herpetic neuralgia, diabetic neuropathy, sciatica, back pain, head or neck pain, severe or intractable pain, breakthrough pain, post-surgical pain, hereditary erythromelalgia, dental pain, rhinitis, cancer pain, complex regional pain syndrome (CRPS), inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and bladder disorders.

[0083] In one embodiment, the functional pain syndrome is selected from the group consisting of chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome, abdominal pain, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome and Gulf War syndrome.

[0084] In one embodiment, the cancer pain is associated with a cancer selected from the group consisting of endometrial cancer, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, non-small cell lung cancer, brain cancer, a leukemia, a lymphoma, bone cancer and pain associated with metastasis of a cancer.

[0085] In one embodiment, the antibody or antigen-binding fragment is administered to the patient in combination with a second therapeutic agent.

[0086] In one embodiment, the second therapeutic agent is selected from the group consisting of an opioid, a COX-2 inhibitor, a local anesthetic, an NMDA modulator, a cannabinoid receptor agonist, a P2X family modulator, a VR1 antagonist, a substance P antagonist, a second GFR α 3 antagonist, a cytokine or cytokine receptor antagonist, a nerve growth factor (NGF) inhibitor (a small molecular inhibitor or an anti-NGF antibody), aspirin, a NSAID, a steroid, morphine, a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), a tricyclic, an inhibitor of a voltage-gated sodium channel (Na_v), a calcium channel inhibitor, a potassium channel inhibitor, a tumor necrosis factor (TNF) or TNF receptor inhibitor, an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis), a RET inhibitor, an inhibitor of a GDNF family ligand, an inhibitor of an acid sensing ion channel (ASIC1 or ASIC3), an anti-convulsant (gabapentin or pregabalin), an inhibitor of a prekineticin receptor (PROK1 and PROK2), a caspase inhibitor, a p38 inhibitor, an IKK1/2 inhibitor, CTLA-4Ig and a corticosteroid.

[0087] In one embodiment, the second GFR α 3 antagonist is a small organic molecule, a second antibody specific for GFR α 3, a polypeptide antagonist, a siRNA or an antisense molecule specific for GFR α 3.

[0088] In one embodiment, the cytokine or cytokine receptor antagonist is an interleukin-1 (IL-1) antagonist, an IL-6 antagonist, or an IL-18 antagonist.

[0089] The disorder treated is any disease or condition, which is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of hGFR α 3 activity. Specific populations treatable by the therapeutic methods described herein include a disease, disorder, or condition selected from acute, chronic, ischemic, neuropathic, or inflammatory pain, hypersensitivity, such as visceral, thermal, or mechanical hypersensitivity, chronic pancreatitis, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epileptic conditions, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, inflammatory bowel disease, spleen inflammation, stomach pain, trigonitis, fibroids, peritonitis, faecal urgency, incontinence, rectal hypersensitivity, visceral pain, osteoarthritis pain, post-herpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, breakthrough pain, post-surgical pain, cancer pain, or chemotherapy-induced pain. Other conditions treatable by the therapeutic methods described herein include Hirschsprung disease, hereditary erythromelalgia, bladder disorders, rhinitis, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, a hematologic (blood-borne) cancer, such as a leukemia or a lymphoma, bone cancer, or pain associated with metastasis of a cancer, for example, pain associated with metastasis of a cancer to the bone. The antibodies of the invention or antigen-binding fragments thereof may also be used to treat the following conditions: non-malignant acute, chronic, or fracture bone pain; rheumatoid arthritis, spinal stenosis; neuropathic low back pain; myofascial pain syndrome; pancreatic; chronic headache pain; tension headache; diabetic neuropathy; HIV-associated neuropathy; Charcot-Marie Tooth

neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome (CRPS, also known as Reflex Sympathetic Dystrophy); phantom pain; intractable pain; acute musculoskeletal pain; joint pain; acute gout pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; burn and trauma pain; endometriosis; herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis pain; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebotic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; Fabry's disease pain; bladder and urogenital disease; and hyperactivity bladder. In one embodiment the antibodies of the invention may be used to treat a functional pain syndrome, wherein the functional pain syndrome is selected from the group consisting of chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome, abdominal pain, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome and Gulf War syndrome.

[0090] The antibodies of the invention or antigen-binding fragments thereof may also be used to inhibit tumor cell growth/proliferation, or metastasis of tumor cells. In certain embodiments, the antibodies of the invention or antigen-binding fragments thereof, may be used to treat a cancer, or the "pain associated with a cancer" or "cancer-associated pain", including, for example, but not limited to, endometrial cancer, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, a hematologic (blood-borne) cancer, such as a leukemia or a lymphoma, bone cancer, or pain associated with metastasis of a cancer, for example, pain associated with metastasis of a cancer to the bone. "Cancer-associated pain" also includes pain more generally associated with cancerous conditions such as, e.g., renal cell carcinoma, pancreatic carcinoma, head and neck cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, malignant mesothelioma, multiple myeloma, synovial sarcoma, thyroid cancer, or melanoma. The antibodies of the present invention are also useful for treating or preventing pain caused by or associated with cancer therapy or anti-cancer medical treatments, e.g., chemotherapy-induced neuropathic pain such as pain caused by or associated with treatment with paclitaxel (Taxol™), docetaxel (Taxotere®); nitrosourea, cyclophosphamide, doxorubicin, epirubicin, 5-fluorouracil, topotecan, irinotecan, carmustine, estramustine, and platinum-based chemotherapeutic compounds, such as cisplatin, carboplatin, and iproplatin.

[0091] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0092]

Figure 1. Inhibition of artemin-sensitized capsaicin thermal hyperalgesia in animals injected with mouse GFR α 3 antibodies (indirect blocker M1 M6977N or direct blocker M1 M6986N, n=8 each) or isotype (negative) control antibody (M2M180N, n=8) at 30mg/kg s.c. 2 days before receiving capsaicin (1 day before receiving 0.5 μ g artemin).

Figure 2A and 2B. Tactile allodynia measured by von Frey Hairs in animals from two experiments (A & B) injected with fibrosarcoma and treated with isotype (negative) control antibody (M2M180N) or M1M6977N or M1M6986N anti-mouse GFR α 3 antibodies (n=8-11 per group). *p<.05, **p<.01, or ***p<.001 compared to isotype control at the same time point.

Figure 3A and 3B. Percent ipsilateral weight bearing in animals from two experiments (A & B) injected with fibrosarcoma and treated with isotype (negative) control (M2M180N) or M1 M6977N or M1 M6986N anti-mouse GFR α 3 antibodies (n=8-11 per group).

Figure 4A and 4B. Guarding scores in animals from two experiments (A & B) injected with fibrosarcoma cells and treated with isotype (negative) control (M2M180N) or M1 M6977N or M1 M6986N anti-mouse GFR α 3 antibodies (n=8-11 per group). **p<.01 compared to isotype control at the same time point.

Figure 5. Tactile allodynia measured by von Frey Hairs in animals injected with carcinoma and treated with isotype (negative) control (M2M180N) or M1 M6977N or M1 M6986N anti-mouse GFR α 3 antibodies (n=9-10 per group). *p<.05, **p<.01, or ***p<.001 compared to isotype (negative) control at the same time point.

Figure 6A and 6B. Percent ipsilateral weight bearing at two time points (A=11 days & B=18 days) injected with carcinoma and treated with isotype (negative) control (M2M180N) or M1 M6977N or M1 M6986N anti-mouse GFR α 3 antibodies (n=9-10 per group). *p<.05 compared to isotype control antibody by post hoc Dunnett's analysis.

Figure 7. Guarding scores in animals injected with carcinoma and treated with isotype (negative) control (M2M180N) or M1M6977N or M1M6986N anti-mouse GFR α 3 antibodies (n=9-10 per group). *p<.05, ***p<.001 compared to isotype control at the same time point.

Figure 8. Tactile allodynia measured by von Frey Hairs in animals with DMM treated with isotype (negative) control (M2M180N) or M1M6977N or M1M6986N anti-mouse GFR α 3 antibodies (n=10 per group). **p<.01 or ***p<.001 compared to isotype control at the same time point.

Figure 9. Cross-Competition Analysis of anti-GFR α 3 Antibodies for Binding to Biotin-hGFR α 3-mmH.

DETAILED DESCRIPTION

[0093] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions 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 be limiting, since the scope of the present invention will be limited only by the appended claims.

[0094] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described.

Definitions

[0095] "GFR α 3," or "hGFR α 3", as used herein, refers to the glycosylphosphatidylinositol (GPI)-anchored protein receptor for artemin, which belongs to the family of glial cell line derived neurotrophic factors (GDNF). It is one of the GDNF family receptor alpha proteins that, once bound to its ligand, artemin, mediates activation of the receptor tyrosine kinase RET ("rearranged during transfection"). Four members of the GFR α family have been recognized to date, GFR α -1-4 (Lindsay RM et al., Neuron, (1996), 17:571-574; Airaksinen, MS, et al., Mol. Cell Neurosci., (1999), 13:313-325). GFR α 3 is also known in the art as GDNF family receptor alpha 3 GPI-linked receptor, or glial cell line-derived neurotrophic factor receptor alpha-3. The expression "GFR α 3," or "hGFR α 3", or fragments thereof, as used herein, refers to the human GFR α 3 protein or fragment thereof, unless specified as being from a non-human species, e.g. "mouse GFR α 3", "rat GFR α 3", or "monkey GFR α 3". Moreover, "GFR α 3," or "hGFR α 3", as used herein, refers to human GFR α 3 encoded by the nucleic acid sequence shown in SEQ ID NO: 374 (Genbank accession number NM_001496) and has the amino acid sequence as shown in SEQ ID NO: 375 (Genbank accession number NP_001487.2), or a biologically active fragment thereof. The signal sequence spans amino acid residues 1-31 of SEQ ID NO: 375, the mature protein spans amino acid residues 32-382 of SEQ ID NO: 375, whereas the C-terminal Pro region spans amino acid residues 383-400 of SEQ ID NO: 375. The GPI cleavage site is found at amino acid residue 374 of SEQ ID NO: 375 (asparagine). The amino acid sequence of human artemin is found in Genbank as accession number Q5T4W7 and the amino acid sequence of human artemin (from amino acids A108-G220 of accession number Q5T4W7) with a myc-myc-hexahistidine tag is shown as SEQ ID NO: 369 (with amino acid residues 114-141 of SEQ ID NO: 369 being the myc-myc hexahistidine tag).

[0096] Although GFR α 3 is structurally and functionally similar to the other members of the GFR α family, GFR α 3 is the most distantly related of the four family members. GFR α 1 and

GFR α 2 share about 50% identity (Sanicola, M. et al., PNAS, USA, (1997), 94:6238-43; Klein, RD, et al., (1997), Nature, 387:717-21; Buj-Bello, A. et al., Nature (1997), 387:721-4; Baloh, RH, et al., Neuron, (1997), 18:793-802), while GFR α 3 has only 32 and 37% identity, respectively, with these proteins (Masure, S. et al., Eur. J. Biochem., (1998), 251:622-30; Nomoto, S. et al., BBRC, (1998), 244:849-53). The amino acid sequence of mouse GFR α 3 has the following Genbank Accession Number: NP_034410.3. The amino acid sequence of human GFR α 1 has the following Genbank Accession Number: NP_005255.1 and is also found as SEQ ID NO: 376. The amino acid sequence of cynomolgus GFR α 3 is shown in SEQ ID NO: 377 and the amino acid sequence of cynomolgus RET is shown in SEQ ID NO: 378.

[0097] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds (*i.e.*, "full antibody molecules"), as well as multimers thereof (*e.g.* IgM) or antigen-binding fragments thereof. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "V_H") and a heavy chain constant region (comprised of domains C_H1, C_H2 and C_H3). Each light chain is comprised of a light chain variable region ("LCVR" or "V_L") and a light chain constant region (C_L). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In certain embodiments of the invention, the FRs of the anti-GFR α 3 antibody (or antigen binding fragment thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0098] Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan et al. (1995 FASEB J. 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos et al. 2002 J Mol Biol 320:415-428).

[0099] CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDRH2 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue(s) thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

[0100] The fully-human anti-hGFR α 3 antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of

the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are back-mutated to the corresponding germline residue(s) or to a conservative amino acid substitution (natural or non-natural) of the corresponding germline residue(s) (such sequence changes are referred to herein as "germline back-mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline back-mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the germline sequence. In other embodiments, only certain residues are mutated back to the germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or to germline back-mutations within all framework regions FR1, FR2, FR3, FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. Furthermore, the antibodies of the present invention may contain any combination of two or more germline back-mutations within the framework and/or CDR regions, *i.e.*, wherein certain individual residues are mutated back to the germline sequence while certain other residues that differ from the germline sequence are maintained. Once obtained, antibodies and antigen-binding fragments that contain one or more germline back-mutations can be easily tested for one or more desired properties such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

[0101] The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (e.g., mouse), have been grafted onto human FR sequences. The anti-human GFR α 3 antibodies of the invention may be designated as "anti-hGFR α 3" or "anti-GFR α 3".

[0102] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about 1×10^{-6} M or less (e.g., a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. An isolated antibody that specifically binds hGFR α 3 may, however, exhibit cross-reactivity to other antigens such as

GFR α 3 molecules from other species. Moreover, multi-specific antibodies that bind to hGFR α 3 and one or more additional antigens or a bi-specific that binds to two different regions of hGFR α 3 are nonetheless considered antibodies that "specifically bind" hGFR α 3, as used herein.

[0103] As used herein, the term "does not bind" to a specified target molecule (e.g. a particular GFR α 3 peptide) means that the antibody, when tested for binding to the target molecule at 25°C in a Plasmon resonance assay, exhibits a K_D of greater than 500 nM, or if tested for binding to the target molecule at 25°C in an enzyme linked immunosorbent assay (ELISA) exhibits an EC_{50} of greater than 50 nM, or fails to exhibit any binding in either type of assay or equivalent thereof.

[0104] The term "high affinity" antibody refers to those mAbs having a binding affinity to hGFR α 3 of at least 10^{-9} M; preferably 10^{-10} M; more preferably 10^{-11} M, even more preferably 10^{-12} M, as measured by surface plasmon resonance, e.g., BIACORE™ or solution-affinity ELISA.

[0105] By the term "slow off rate", "Koff" or "kd" is meant an antibody that dissociates from hGFR α 3 with a rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, preferably $1 \times 10^{-4} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance, e.g., BIACORE™.

[0106] The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to hGFR α 3.

[0107] The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety ("immunoconjugate"), such as an opioid, a COX-2 inhibitor, a local anesthetic, a cytokine antagonist, such as an IL-1 or IL-6 inhibitor, a second GFR α 3 inhibitor, an NMDA modulator, a cannabinoid receptor agonist, a P2X family modulator, a VR1 antagonist, a substance P antagonist, a chemotherapeutic agent, or a radioisotope.

[0108] An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies (Abs) having different antigenic specificities (e.g., an isolated antibody that specifically binds hGFR α 3, or a fragment thereof, is substantially free of Abs that specifically bind antigens other than hGFR α 3).

[0109] A "neutralizing antibody", as used herein (or an "antibody that neutralizes GFR α 3 activity"), is intended to refer to an antibody whose binding to hGFR α 3 results in inhibition of at least one biological activity of GFR α 3. This inhibition of the biological activity of GFR α 3 can be assessed by measuring one or more indicators of GFR α 3 biological activity by one or more of

several standard *in vitro* or *in vivo* assays known in the art (see examples below).

[0110] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

[0111] The term " K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0112] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope" also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[0113] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0114] As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 98% or 99% sequence identity. Preferably, residue positions, which are not identical, differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted

upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art (See, e.g., Pearson (1994) *Methods Mol. Biol.* 24: 307-331). Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (See Gonnet *et al.*, *Science*, (1992), 256:1443 45). A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0115] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. (See, e.g., Altschul *et al.* (1990) *J. Mol. Biol.* 215: 403 410 and (1997) *Nucleic Acids Res.* 25:3389 402).

[0116] In specific embodiments, the antibody or antibody fragment for use in the described herein may be mono-specific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise an Y96F modification (by IMGT;

Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 mAbs; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 mAbs; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 mAbs. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

[0117] By the phrase "therapeutically effective amount" is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) *The Art, Science and Technology of Pharmaceutical Compounding*).

[0118] The term "functional pain syndrome(s)", refers to chronic symptom-based syndromes that affect up to 15% of the population worldwide. They are characterized by chronic pain and discomfort referred to in different regions of the body. No generally agreed-upon structural, inflammatory, or biochemical abnormalities have been identified that could fully explain the symptoms. Patients show a greatly reduced quality of life, yet treatment options are limited, and the development of novel therapeutic approaches has been disappointing. Some of the common disorders, which fall into this category, include chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome, functional abdominal pain syndrome, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional rectal pain syndrome, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome, and Gulf War syndrome.

General Description

[0119] The glial cell line-derived neurotrophic factor related family includes glial cell line-derived neurotrophic factor (GDNF), neurturin (NRTN), persephin (PSPN), and artemin (ARTN). GDNF family proteins are differentially involved in the development and maintenance of sensory, enteric, sympathetic and parasympathetic neurons and a variety of non-neural tissues (Henderson, C.E., et al., (1994), *Science* 266:1062-1064; Kotzbauer, P.T. et al., (1996), *Nature* 384:467-470; Springer, J.E., et al. (1994), *Exp. Neurol.* 127:167-170; Schaar. D.G., et al., (1993), *Exp. Neurol.* 124:368-371). GDNF is an especially potent survival factor for dopaminergic, noradrenergic and spinal motor neurons (Yan, Q. et al. (1995), *Nature*, 373:341-344; Henderson, C.E., et al., (1994), *Science*, 266:1062-1064; Buj-Bello, A. et al., (1995), *Neuron*, 15:821-828). Other GDNF family growth members have functions outside the nervous system (Trupp, M. et al., (1995), *J. Cell Biol.* 130:137-148; Kotzbauer, P.T. et al., (1996), *Nature* 384:467-470; Springer, J.E., et al. (1994), *Exp. Neurol.* 127:167-170; Schaar. D.G., et al., (1993), *Exp. Neurol.* 124:368-371). For example, NRTN, ARTN, and PSPN are also expressed in the developing kidney. GDNF also has critical roles outside the nervous system in the

regulation of kidney morphogenesis and spermatogenesis (Airaksinen, M.S. et al., (2002), Nature Reviews 3:383-392).

[0120] Each member of the GDNF family binds preferentially to (i.e., is a ligand for) a glycosylphosphatidylinositol (GPI)-anchored protein receptor dynamically associated with the plasma membrane. The GDNF-family receptor alpha family is composed of four different receptors: GFRalpha1 (GFR α 1, GDNFR-alpha); GFRalpha2 (GFR α 2/TrnR2/GDNFR-beta/NTNR-alpha/RETL2); GFRalpha3 (GFR α 3); and GFRalpha4 (GFR α 4). GDNF binds preferentially to GFR α 1, NRTN binds preferentially to GFR α 2, ARTN binds preferentially to GFR α 3 and PSPN binds preferentially to GFR α 4 (Airaksinen, M.S., et al. Nature Reviews Neuroscience (2002), 3:383-394).

[0121] GFR α 2 is highly expressed in cortex, basal forebrain, and specific layers of the olfactory bulb, and poorly expressed in substantia nigra, cerebellum, and motor nuclei. GFR α 3 is expressed in fetal and adult mouse nerves, sympathetic and sensory ganglia, intestine, heart, brain, lung and kidney. GFR α 4 is expressed at low levels in different brain areas in the adult as well as in some peripheral tissues including testis and heart. While the GDNF family member binding preferences are shown above to be GDNF to GFR α 1; neurturin to GFR α 2; artemin to GFR α 3; and persephin to GFR α 4, the ligand receptor pairing is not stringent (Airaksinen, M.S., et al. Nature Reviews Neuroscience (2002), 3:383-394). For example, GDNF binds to GFR α 2 and GFR α 3 with lower efficiencies than it binds to GFR α 1.

[0122] The GDNF family ligands, typically but not exclusively, transmit their signals through multi-component complexes composed of a ligand, its GFR alpha receptor and the receptor tyrosine kinase, c-Ret. Ret is a common element of these ligand signaling complexes. Ret is a proto-oncogene that strongly activates anti-apoptotic signals through the activation of the phosphoinositol-3 kinases (PI3-K)/PDK/AKT(PKB) and the Ras/Raf/MEK/ERK pathways. Ret is also able to activate phospholipase C gamma (PLCgamma) which elevates intracellular calcium and facilitates activation of members of the conventional and novel protein kinase C (PKC) family. GDNF family ligand receptor complexes are not restricted to signaling through Ret. GDNF:GFRalpha1 can bind to NCAM in cells lacking RET and activate Fyn and FAK. Under some conditions GDNF:GFRalpha complexes directly activate src kinase.

[0123] In certain embodiments of the present invention, any one or more of the three globular cysteine-rich domains (1, 2, or 3) of GFR α 3, or a fragment thereof, may be used to prepare antibodies that bind GFR α 3 and inhibit its function, or inhibit its ability to bind its ligand, such as, artemin. In certain embodiments, an antibody of the invention specific for GFR α 3 may bind to a ligand-binding domain on GFR α 3, and as such, may block the binding of the ligand (artemin)-GFR α 3 complex to RET. The full-length amino acid sequence of human GFR α 3 is shown as SEQ ID NO: 375. The nucleic acid encoding human GFR α 3 is shown in SEQ ID NO: 374. Domain 1 spans residues 44-124 of SEQ ID NO: 375; domain 2 spans residues 162-239 of SEQ ID NO: 375; domain 3 spans residues 248-340 of SEQ ID NO: 375. (See either SEQ ID NO. 375 or Genbank NP_001487.2).

[0124] Any of these domains, 1, 2, or 3, or fragments derived therefrom, may be used to prepare antibodies that bind specifically to GFR α 3 and inhibit its activity, or at least one function associated with GFR α 3. In certain embodiments, the antibodies of the invention bind specifically to GFR α 3 and may prevent signaling mediated by GFR α 3. In certain embodiments, the antibodies that bind specifically to GFR α 3 may prevent binding of GFR α 3 to its ligand, such as artemin (Wang, X. et al. Structure, (2006), 14:1083-1092). In certain embodiments, the antibodies that bind specifically to GFR α 3 may prevent activation of the RET receptor tyrosine kinase. In certain embodiments, the antibodies of the invention may bind specifically to GFR α 3 without preventing activation of the RET receptor tyrosine kinase. In certain embodiments, the antibodies of the invention may bind specifically to GFR α 3 and prevent signaling through RET, or through a mediator other than RET. In certain embodiments, the antibodies of the invention may be used to inhibit tumor cell growth/proliferation and as such, may be useful for treating certain cancers/malignancies, or the pain associated with such cancers/malignancies, or the pain associated with metastasis of such cancers/malignancies (See Tang, J-Z, et al. Mol Cancer Ther (2010), 9(6): 1697-1708; Kang, J. et al. Oncogene, (2009), 28:2034-2045; Ceyhan, G.O. et al. Annals of Surgery, (2006), 244(2):274-281; Banerjee, A., et al. Breast Cancer Res (2011), 13:R112; Pandey, V. et al., Endocrinology, (2010), 151(3):909-920; Kang, J. et al., Oncogene, (2010), 29:3228-3240; Li, S. et al. J Biomed Sci (2011), 18:24). In certain embodiments, antibodies that bind specifically to GFR α 3 may be prepared using fragments of the above-noted regions, or peptides that extend beyond the designated regions by about 10 to about 50 amino acid residues from either, or both, the N or C terminal ends of the regions described herein. In certain embodiments, any combination of the above-noted regions or fragments thereof may be used in the preparation of GFR α 3 specific antibodies. As noted above, the length, or the number of amino acid residues encompassing the three domains of hGFR α 3 may vary by about ten to fifty amino acid residues extending from either, or both, the N terminal or C terminal end of the full length domain, or a fragment thereof, for preparation of anti-hGFR α 3 specific antibodies.

Antigen-Binding Fragments of Antibodies

[0125] Unless specifically indicated otherwise, the term "antibody," as used herein, shall be understood to encompass antibody molecules comprising two immunoglobulin heavy chains and two immunoglobulin light chains (*i.e.*, "full antibody molecules") as well as antigen-binding fragments thereof. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to hGFR α 3. An antibody fragment may include a Fab fragment, a F(ab')₂ fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA

encoding antibody variable and (optionally) constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0126] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) $F(ab')_2$ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR)). Other engineered molecules, such as diabodies, triabodies, tetrabodies and minibodies, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0127] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain $V_H - V_H$, $V_H - V_L$ or $V_L - V_L$ dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0128] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) $V_H - C_H1$; (ii) $V_H - C_H2$; (iii) $V_H - C_H3$; (iv) $V_H - C_H1 - C_H2$; (v) $V_H - C_H1 - C_H2 - C_H3$; (vi) $V_H - C_H2 - C_H3$; (vii) $V_H - C_L$; (viii) $V_L - C_H1$; (ix) $V_L - C_H2$; (x) $V_L - C_H3$; (xi) $V_L - C_H1 - C_H2$; (xii) $V_L - C_H1 - C_H2 - C_H3$; (xiii) $V_L - C_H2 - C_H3$; and (xiv) $V_L - C_L$. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (e.g., by disulfide bond(s)).

[0129] As with full antibody molecules, antigen-binding fragments may be mono-specific or multi-specific (e.g., bi-specific). A multi-specific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is

capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multi-specific antibody format, including the exemplary bi-specific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

Preparation of Human Antibodies

[0130] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human GFR α 3.

[0131] Using VELOCIMMUNE™ technology or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to GFR α 3 are initially isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0132] In general, the antibodies of the instant invention possess very high affinities, typically possessing K_D of from about 10^{-13} through about 10^{-8} M, or from about 10^{-12} through about 10^{-9} M when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Bioequivalents

[0133] The anti-GFR α 3 antibodies and antibody fragments described herein encompass proteins having amino acid sequences that vary from those of the described antibodies, but that retain the ability to bind human GFR α 3. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the anti-GFR α 3 antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an anti-GFR α 3 antibody or antibody fragment that is essentially bioequivalent to an anti-GFR α 3 antibody or antibody fragment of the invention.

[0134] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either as a single dose or as multiple doses. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

[0135] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0136] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0137] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0138] Bioequivalence may be demonstrated by *in vivo* and/or *in vitro* methods. Bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[0139] Bioequivalent variants of anti-GFR α 3 antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include anti-GFR α 3 antibody variants comprising amino acid changes, which modify the glycosylation characteristics of the antibodies, e.g., mutations which eliminate or remove glycosylation.

Anti-GFR α 3 Antibodies Comprising Fc Variants

[0140] According to certain embodiments of the present invention, anti-GFR α 3 antibodies are provided comprising an Fc domain comprising one or more mutations, which enhance or diminish antibody binding to the FcRn receptor, e.g., at acidic pH as compared to neutral pH. For example, the present invention includes anti-GFR α 3 antibodies comprising a mutation in the C_H2 or a C_H3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (e.g., in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, e.g., a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (e.g., H/F or Y); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 259I (e.g., V259I), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a 252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P).

[0141] For example, the present invention includes anti-GFR α 3 antibodies comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (e.g., T250Q and M248L); 252Y, 254T and 256E (e.g., M252Y, S254T and T256E); 428L and 434S (e.g., M428L and N434S); and 433K and 434F (e.g., H433K and N434F). All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present invention.

Biological Characteristics of the Antibodies

[0142] In general, the antibodies of the present invention may function by binding to any one or more of the three globular cysteine-rich domains (1, 2, or 3) of hGFR α 3. In certain embodiments, the antibodies of the present invention may bind to an epitope located on at least one of the cysteine-rich domains of hGFR α 3. In certain embodiments, an antibody of the invention may bind to amino acid residues of domain 1 of GFR α 3, ranging from about residue 44 to about residue 124 of SEQ ID NO: 375. In certain embodiments, an antibody of the invention may bind to amino acid residues of domain 2 of GFR α 3, ranging from about residue 162 to about residue 239 of SEQ ID NO: 375. In certain embodiments, an antibody of the invention may bind to amino acid residues of domain 3 of GFR α 3, ranging from about residue 248 to about residue 340 of SEQ ID NO: 375. In certain embodiments, the antibodies of the present invention may function by blocking or inhibiting GFR α 3 activity by binding to a region in any one of the domains that acts as the ligand binding domain, thus preventing binding of the ligand, such as, artemin, to that site. In certain embodiments, an antibody of the invention may bind to the ligand binding site on one of the domains of GFR α 3 and prevent subsequent

binding of the artemin-GFR α 3 complex to RET. In one embodiment, an antibody of the invention may bind to any one or more of the epitopes in the artemin-GFR α 3 complex that may determine or play a role in the specificity between ligand and GFR α 3, such as in the region ranging from residues 167-184 of SEQ ID NO: 375. In certain embodiments, an antibody of the invention may bind to one or more of the residues of domain 2 that are responsible for the specificity between artemin and GFR α 3, for example, the amino acid residues at positions 167 (met), 176 (asp) and/or position 184 (glu), of SEQ ID NO: 375 and in so binding, may prevent ligand binding to its receptor, and subsequently may prevent signaling through the RET receptor tyrosine kinase, or through a signaling mediator or modulator other than RET. In certain embodiments, the antibodies of the invention may bind to the membrane bound form of GFR α 3 or to the soluble form of GFR α 3. In certain embodiments, the antibodies of the invention may bind GFR α 3, but do not cross react with GFR α 1, GFR α 2, or GFR α 4. In certain embodiments, the antibodies of the present invention may be bi-specific antibodies. The bi-specific antibodies of the invention may bind one epitope in one cysteine rich region of one domain and may also bind one cysteine-rich region in a second domain of hGFR α 3. In certain embodiments, the bi-specific antibodies of the invention may bind to two different regions within the same domain. In certain embodiments, one arm of a bi-specific antibody of the invention may bind to one cysteine rich region of one domain of hGFR α 3 and the other arm may bind to RET, or to a modulator other than RET. In certain embodiments, the bispecific antibodies may bind one domain in GFR α 3 and one domain in GFR α 1 or GFR α 2.

[0143] More specifically, the anti-GFR α 3 antibodies of the invention may exhibit one or more of the following characteristics:

1. (i) exhibits a K_D ranging from about 10^{-8} M to about 10^{-13} M as measured by surface plasmon resonance;
2. (ii) demonstrates the ability to block about 50-100% of the binding of GFR α 3 to its ligand, artemin, with an IC_{50} value ranging from about 40 pM to about 15 nM;
3. (iii) demonstrates the ability to block about 20% to about 100% of the binding of GFR α 3 to a solid support coated with a mixture of artemin and RET;
4. (iv) blocks or inhibits artemin-dependent activation of RET with an IC_{50} ranging from about 200 pM to about 50 nM;
5. (v) inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain;
6. (vi) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo*;
7. (vii) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis; or
8. (viii) does not cross-react with other GFR co-receptors for RET.

[0144] Certain anti-GFR α 3 antibodies of the present invention are able to inhibit or attenuate GFR α 3 activity in an *in vitro* assay. The ability of the antibodies of the invention to bind to and inhibit the binding of GFR α 3 to its ligand artemin alone or in the presence of RET may be measured using any standard method known to those skilled in the art, including binding

assays, or assays to determine if the antibodies block the activation of RET by inhibiting the binding of GFR α 3 to its receptor artemin, such as those described herein. Non-limiting, exemplary *in vitro* assays for measuring GFR α 3 activity are illustrated in Examples 4 and 5, below.

[0145] The present invention includes anti-GFR α 3 antibodies and antigen binding fragments thereof which bind to one or more of the cysteine rich globular domains of GFR α 3, as shown in SEQ ID NO: 375, or to a fragment thereof. The antibodies specific for GFR α 3 may contain no additional labels or moieties, or they may contain an N-terminal or C-terminal label or moiety. In one embodiment, the label or moiety is biotin. In a binding assay, the location of a label (if any) may determine the orientation of the peptide relative to the surface upon which the peptide is bound. For example, if a surface is coated with avidin, a peptide containing an N-terminal biotin will be oriented such that the C-terminal portion of the peptide will be distal to the surface.

[0146] Described herein is a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds hGFR α 3 and neutralizes hGFR α 3 activity, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 and 397; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs : 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 389 and 405; (iii) comprises any one or more of the heavy or light chain CDR1, CDR2, and CDR3 sequences depicted in Table 1 and combinations thereof; (iv) is specific for binding to and/or blocking GFR α 3 activity without binding to and/or blocking other GFR alpha receptors, including GFR α 1, GFR α 2 and GFR α 4; (v) demonstrates binding specificity for any one or more of the cysteine-rich globular domains of GFR α 3; (vi) blocks activation of and signaling through the RET receptor tyrosine kinase; (vii) inhibits or reduces artemin-sensitized thermal hyperalgesia *in vivo*; (viii) inhibits or reduces allodynia in an *in vivo* model of osteoarthritis; or inhibits or reduces one or more nociceptive responses in an *in vivo* model of bone cancer pain.

Epitope Mapping and Related Technologies

[0147] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques include, for example, a routine cross-blocking assay such as that described Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY) can be performed. Other methods include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol Biol 248:443-63), peptide cleavage analysis crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Protein Science 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected

by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than exchangeable protons within amino acids that are not part of the interface. As a result, amino acids that form part of the protein/antibody interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues that correspond to the specific amino acids with which the antibody interacts. See, e.g., Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem.* 73:256A-265A.

[0148] The term "epitope" refers to a site on an antigen to which B and/or T cells respond. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[0149] Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (See, e.g., US 2004/0101920). Each category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones that produce mAbs having the desired characteristics. MAP may be used to sort the antibodies of the invention into groups of antibodies binding different epitopes.

[0150] In certain embodiments, the anti-GFR α 3 antibody or antigen-binding fragment of an antibody binds an epitope within at least one of the GFR α 3 cysteine rich domains 1, 2, or 3, or a fragment thereof, wherein domain 1 ranges from about residue number 44 to about residue number 124 of SEQ ID NO: 375; domain 2 ranges from about residue number 162 to about residue number 239 of SEQ ID NO: 375; domain 3 ranges from about residue number 248 to about residue number 340 of SEQ ID NO: 375.

[0151] In certain embodiments, the anti-GFR α 3 antibody or antigen-binding fragment of an antibody binds an epitope within domain 1, or a fragment thereof, of human GFR α 3.

[0152] In certain embodiments, the anti-GFR α 3 antibody or antigen-binding fragment of an antibody binds an epitope within domain 2, or a fragment thereof, of human GFR α 3.

[0153] In certain embodiments, the anti-GFR α 3 antibody or antigen-binding fragment of an antibody binds an epitope within domain 3, or a fragment thereof, of human GFR α 3.

[0154] In certain embodiments, the antibody or antibody fragment binds an epitope, which includes more than one of the enumerated epitopes of GFR α 3 within domain 1, 2, or 3, and/or within two different domains (for example, epitopes within the 1 and 2 domains, or within the 2 and 3 domains, or within the 1 and 3 domains).

[0155] In certain embodiments, the antibody is a bi-specific antibody that binds one epitope within one domain of GFR α 3 and another epitope within a different domain of GFR α 3. In one embodiment, the antibody is a bi-specific antibody that binds one epitope in domain 1 of GFR α 3 and another epitope in domain 2 of GFR α 3. In one embodiment, the antibody is a bi-specific antibody that binds one epitope in domain 1 of GFR α 3 and another epitope within domain 3 of GFR α 3. In one embodiment, the antibody is a bi-specific antibody that binds one epitope in domain 2 of GFR α 3 and another epitope within domain 3 of GFR α 3.

[0156] The present invention includes anti-GFR α 3 antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein (e.g., H4H2207N, H4H2212N, H4H2236N3, H4H2243N2, H4H2210N, H4H2234N, H4H2291S, H4H2292S, H4H2293P, H4H2294S, H4H2295S, H4H2296S, H4H2341S, H4H2342P, H4H2344S, H4H2345S, H4H2346S, H4H2350P, H4H2352S, H4H2354S, H4H2355S, H4H2357S, H4H2364S, H1M2243N and H1M2236N). Likewise, the present invention also includes anti-GFR α 3 antibodies that compete for binding to GFR α 3 or a GFR α 3 fragment with any of the specific exemplary antibodies described herein.

[0157] One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-GFR α 3 antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-GFR α 3 antibody of the invention, the reference antibody is allowed to bind to a GFR α 3 protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the GFR α 3 molecule is assessed. If the test antibody is able to bind to GFR α 3 following saturation binding with the reference anti-GFR α 3 antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-GFR α 3 antibody. On the other hand, if the test antibody is not able to bind to the GFR α 3 molecule following saturation binding with the reference anti-GFR α 3 antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-GFR α 3 antibody of the invention.

[0158] To determine if an antibody competes for binding with a reference anti-GFR α 3 antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a GFR α 3 molecule under saturating conditions followed by assessment of binding of the test antibody to the GFR α 3 molecule. In a second orientation, the test antibody is allowed to bind to a GFR α 3 molecule under saturating conditions followed by assessment of binding of the reference antibody to the GFR α 3 molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the GFR α 3

molecule, then it is concluded that the test antibody and the reference antibody compete for binding to GFR α 3. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the identical epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

[0159] Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990 50:1495-1502). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0160] Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art.

Species Selectivity and Species Cross-Reactivity

[0161] According to certain embodiments of the invention, the anti-GFR α 3 antibodies bind to human GFR α 3 but not to GFR α 3 from other species. Alternatively, the anti-GFR α 3 antibodies of the invention, in certain embodiments, bind to human GFR α 3 and to GFR α 3 from one or more non-human species. For example, the anti-GFR α 3 antibodies of the invention may bind to human GFR α 3 and may bind or not bind, as the case may be, to one or more of mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgus, marmoset, rhesus or chimpanzee GFR α 3.

Immunoconjugates

[0162] Described herein is a human anti-GFR α 3 monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as an agent that is capable of reducing pain and/or inflammation, a chemotherapeutic drug, or a radioisotope. The type of therapeutic moiety that may be conjugated to the anti-GFR α 3 antibody will take into account the condition to be treated and the desired therapeutic effect to be achieved. For example, for treating acute or chronic pain, an agent such as an NSAID, an opioid, or a Cox-2 inhibitor, or a local anesthetic agent, or a second GFR α 3 inhibitor may be conjugated to the GFR α 3 antibody. Alternatively, if the desired therapeutic effect is to treat the inflammation associated with a

painful condition, it may be advantageous to conjugate an anti-inflammatory agent to the anti-GFR α 3 antibody, such as, but not limited to, celecoxib, or a cytokine antagonist, such as an IL-1 or an IL-6 inhibitor. If the condition to be treated is a cancerous condition, it may be beneficial to conjugate a chemotherapeutic drug, or a radioisotope to the GFR α 3 antibody. Examples of suitable agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Multi-specific Antibodies

[0163] The antibodies of the present invention may be mono-specific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al., 1991, J. Immunol. 147:60-69; Kufer et al., 2004, Trends Biotechnol. 22:238-244. The anti-GFR α 3 antibodies of the present invention can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bi-specific or a multi-specific antibody with a second binding specificity. For example, the present invention includes bi-specific antibodies wherein one arm of an immunoglobulin is specific for human GFR α 3 or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target or is conjugated to a therapeutic moiety. In certain embodiments of the invention, one arm of an immunoglobulin is specific for an epitope on one domain of hGFR α 3 or a fragment thereof, and the other arm of the immunoglobulin is specific for an epitope on a second domain of hGFR α 3. In certain embodiments, one arm of an immunoglobulin is specific for one epitope on one domain of hGFR α 3 and the other arm is specific for a second epitope on the same domain of hGFR α 3.

[0164] An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody

format described above are contemplated within the scope of the present invention.

Therapeutic Administration and Formulations

[0165] The invention provides therapeutic compositions comprising the anti-GFR α 3 antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0166] The dose of antibody may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. When the antibody of the present invention is used for treating pain associated with GFR α 3 activity in various conditions and diseases, wherein the condition or disease results in acute or chronic pain, inflammatory pain, neuropathic pain, and the like, in an adult patient, it is advantageous to intravenously administer the antibody of the present invention normally at a single dose of about 0.01 to about 20 mg/kg body weight, more preferably about 0.02 to about 7, about 0.03 to about 5, or about 0.05 to about 3 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted.

[0167] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al. (1987) J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0168] The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see, for example, Langer (1990) Science 249:1527-1533).

[0169] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric

materials can be used. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose.

[0170] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0171] A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0172] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.) and the HUMIRA™ Pen (Abbott Labs, Abbott Park, IL), to name only a few.

[0173] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Therapeutic Uses of the Antibodies

[0174] The antibodies of the invention are useful for the treatment, prevention and/or amelioration of any disease, disorder, or condition associated with GFR α 3 activity, or for amelioration of at least one symptom associated with the disease, disorder, or condition, or for alleviating the pain associated with such disease, disorder, or condition. Exemplary conditions, diseases and/or disorders, and/or the pain associated with such conditions, diseases, or disorders, that can be treated with the anti-GFR α 3 antibodies of the present invention include acute, chronic, neuropathic, or inflammatory pain, arthritis, interstitial cystitis, pancreatitis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy or epileptic conditions, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, irritable bowel syndrome, inflammatory bowel syndrome, fecal urgency, incontinence, rectal hypersensitivity, visceral pain, osteoarthritis pain, gout, post-herpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head or neck pain, breakthrough pain, post-surgical pain, cancer pain, including pain associated with bone cancer or pancreatic cancer.

[0175] Other conditions treatable by the therapeutic methods described herein include hereditary erythromelalgia, rhinitis, prostate cancer, breast cancer, bone cancer, cervical cancer, or bladder disorders. The antibodies of the invention or antigen-binding fragments thereof may also be used to treat the following conditions: non-malignant acute, chronic, or fracture bone pain; rheumatoid arthritis, spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; visceral pain, including, abdominal; pancreatic; chronic headache pain; tension headache, including, cluster headaches; diabetic neuropathy; HIV-associated neuropathy; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome (CRPS); phantom pain; intractable pain; musculoskeletal pain; joint pain; acute gout pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; abdominal pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; etc; chest pain, including, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, including, labor pain; cesarean section pain; burn and trauma pain; endometriosis; herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain;

orofacial pain including sinusitis pain, dental pain; multiple sclerosis pain; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebotic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; Fabry's disease pain; bladder and urogenital disease; hyperactivity bladder.

[0176] In one embodiment the antibodies of the invention may be used to treat a functional pain syndrome, wherein the functional pain syndrome is selected from the group consisting of chronic low back pain, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome (CFS), abdominal pain, temporomandibular joint disorder (TMJD), painful bladder syndrome (interstitial cystitis), functional gastrointestinal disorders/syndromes, functional chest pain syndrome, migraines and tension type headaches, chronic pelvic pain syndrome, painful prostate syndrome (chronic prostatitis), multiple chemical sensitivity syndrome and Gulf War syndrome.

[0177] The antibodies of the invention or antigen-binding fragments thereof may also be used to inhibit tumor cell growth/proliferation or metastasis of tumor cells. Accordingly, in certain embodiments, the antibodies of the invention or antigen-binding fragments thereof, may be used to treat a cancer, including, but not limited to, endometrial cancer, prostate cancer, breast cancer, cervical cancer, liver cancer, pancreatic cancer, colon cancer, stomach cancer, uterine cancer, ovarian cancer, kidney cancer, non-small cell lung cancer, brain cancer, a leukemia, a lymphoma, bone cancer, or pain associated with metastasis of a cancer, for example, metastasis of a cancer to the bone. (See Tang, J-Z, et al. *Mol Cancer Ther* (2010), 9(6): 1697-1708; Kang, J. et al. *Oncogene*, (2009), 28:2034-2045; Ceyhan, G.O. et al. *Annals of Surgery*, (2006), 244(2):274-281; Banerjee, A., et al. *Breast Cancer Res* (2011), 13:R112; Pandey, V. et al., *Endocrinology*, (2010), 151(3):909-920; Kang, J. et al., *Oncogene*, (2010), 29:3228-3240; Li, S. et al. *J Biomed Sci* (2011), 18:24).

[0178] The antibodies of the present invention are also useful for treating or preventing cancer-associated pain. "Cancer-associated pain" includes, e.g., bone cancer pain, including pain from cancer that has metastasized to bone (e.g., breast cancer, prostate cancer, lung cancer, sarcoma, kidney cancer, multiple myeloma, etc.). "Cancer-associated pain" also includes pain more generally associated with cancerous conditions such as, e.g., renal cell carcinoma, pancreatic carcinoma, breast cancer, head and neck cancer, prostate cancer, malignant gliomas, osteosarcoma, colorectal cancer, gastric cancer, malignant mesothelioma, multiple myeloma, ovarian cancer, small cell lung cancer, non-small cell lung cancer, synovial sarcoma, thyroid cancer, or melanoma. The antibodies of the present invention are also useful for treating or preventing pain caused by or associated with cancer therapy or anti-cancer medical treatments, e.g., chemotherapy-induced neuropathic pain such as pain caused by or associated with treatment with paclitaxel (Taxol™), docetaxel (Taxotere®); nitrosourea, cyclophosphamide, doxorubicin, epirubicin, 5-fluorouracil, topotecan, irinotecan, carmustine, estramustine, and platinum-based chemotherapeutic compounds, such as cisplatin, carboplatin, and iproplatin.

Combination Therapies

[0179] Combination therapies may include an anti-hGFR α 3 antibody of the invention and, for example, another GFR α 3 antagonist (e.g., anti-GFR α 3 antibody or small molecule inhibitor of GFR α 3); a COX-2 inhibitor; a local anesthetic; an NMDA modulator; a cannabinoid receptor agonist; a P2X family modulator; a VR1 antagonist; a substance P antagonist; an inhibitor of a voltage-gated sodium channel (Na_v), for example, a Na_v1.7 antagonist, or a Na_v1.8 antagonist (e.g., anti-Na_v1.7 or anti-Na_v1.8 antibody or small molecule inhibitor), a Na_v1.9 antagonist (e.g., anti-Na_v1.9 antibody or small molecule inhibitor of Na_v1.9); a calcium channel inhibitor; a potassium channel inhibitor; a cytokine inhibitor or cytokine receptor antagonist (e.g., an interleukin-1 (IL-1) inhibitor (such as rilonacept ("IL-1 trap"; Regeneron) or anakinra (KINERET®, Amgen), a small molecule IL-1 antagonist, or an anti-IL-1 antibody); an IL-18 inhibitor (such as a small molecule IL-18 antagonist or an anti-IL-18 antibody); an IL-6 or IL-6R inhibitor (such as a small molecule IL-6 antagonist, an anti-IL-6 antibody or an anti-IL-6 receptor antibody); an antiepileptic/anti-convulsant drug (e.g., gabapentin, pregabalin); a nerve growth factor (NGF) inhibitor (e.g., a small molecule NGF antagonist or an anti-NGF antibody); an inhibitor of BDNF, TrkA, TrkB or p75; an opioid; morphine; low dose cochlamine; aspirin or another NSAID; steroids (e.g., prednisone, methotrexate, etc.); low dose cyclosporine A; a selective serotonin reuptake inhibitor (SSRI); a serotonin norepinephrine reuptake inhibitor (SNRI); a tricyclic; a tumor necrosis factor (TNF) or TNF receptor inhibitor (e.g., a small molecule TNF or TNFR antagonist or an anti-TNF or TNFR antibody); an inhibitor of TWEAK (TNF-related WEAK inducer of apoptosis); a RET inhibitor; an inhibitor of a GDNF family ligand; an inhibitor of GFR α 1, GFR α 2 or GFR α 4; an inhibitor of an acid sensing ion channel (e.g. ASIC1 or ASIC3; uric acid synthesis inhibitors (e.g., allopurinol); uric acid excretion promoters (e.g., probenecid, sulfinpyrazone, benzbromarone, etc.); an inhibitor of a prekineticin receptor (PROK1 and PROK2); other inflammatory inhibitors (e.g., inhibitors of caspase-1, p38, IKK1/2, CTLA-4lg, etc.); and/or corticosteroids.

Administration Regimens

[0180] Multiple doses of an anti-GFR α 3 antibody may be administered to a subject over a defined time course. The methods described herein comprise sequentially administering to a subject multiple doses of an anti-GFR α 3 antibody. As used herein, "sequentially administering" means that each dose of anti-GFR α 3 antibody is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an anti-GFR α 3 antibody, followed by one or more secondary doses of the anti-GFR α 3 antibody, and optionally followed by one or more tertiary doses of the anti-GFR α 3 antibody.

[0181] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the anti-GFR α 3 antibody. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the

"baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of anti-GFR α 3 antibody, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of anti-GFR α 3 antibody contained in the initial, secondary and/or tertiary doses varies from one another (e.g., adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (e.g., 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (e.g., "maintenance doses").

[0182] For example, each secondary and/or tertiary dose may be administered 1 to 26 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18, 18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of anti- GFR α 3 antibody, which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0183] The methods described herein may comprise administering to a patient any number of secondary and/or tertiary doses of an anti-GFR α 3 antibody. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0184] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient.

Diagnostic Uses of the Antibodies

[0185] The anti-GFR α 3 antibodies of the present invention may also be used to detect and/or measure GFR α 3 in a sample, e.g., for diagnostic purposes. For example, an anti-GFR α 3 antibody, or fragment thereof, may be used to diagnose a condition or disease characterized by

aberrant expression (e.g., over-expression, under-expression, lack of expression, etc.) of GFR α 3. Exemplary diagnostic assays for GFR α 3 may comprise, e.g., contacting a sample, obtained from a patient, with an anti-GFR α 3 antibody of the invention, wherein the anti-GFR α 3 antibody is labeled with a detectable label or reporter molecule. Alternatively, an unlabeled anti-GFR α 3 antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I ; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β -galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure GFR α 3 in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[0186] Samples that can be used in GFR α 3 diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient, which contains detectable quantities of GFR α 3 protein, or fragments thereof, under normal or pathological conditions. Generally, levels of GFR α 3 in a particular sample obtained from a healthy patient (e.g., a patient not afflicted with a disease or condition associated with abnormal GFR α 3 levels or activity) will be measured to initially establish a baseline, or standard, level of GFR α 3. This baseline level of GFR α 3 can then be compared against the levels of GFR α 3 measured in samples obtained from individuals suspected of having a GFR α 3 related disease or condition, or pain associated with such disease or condition.

EXAMPLES

[0187] Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Generation of Human Antibodies to Human GFR α 3

[0188] An immunogen comprising any one of the GFR α 3 peptides having amino acid sequences shown as SEQ ID NOS: 370, 371, 372 and 373, or fragments thereof, may be utilized to generate antibodies to human GFR α 3. These peptides are conjugated to a carrier, for example, KLH, then administered with an adjuvant to stimulate the immune response, to a VELOCIMMUNE® mouse comprising DNA encoding human Immunoglobulin heavy and kappa light chain variable regions. The antibody immune response is monitored by a GFR α 3-specific immunoassay. When a desired immune response is achieved, splenocytes are harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines are screened and selected to identify cell lines that produce GFR α 3-

specific antibodies. Using this technique several anti-GFR α 3 chimeric antibodies (*i.e.*, antibodies possessing human variable domains and mouse constant domains) were obtained. The anti-GFR α 3 antibodies generated using this method were designated H1M2207N, H1M2212N, H1M2236N, H1M2236N3, H1M2243N, H1M2243N2, H1M2210N and H1M2234N.

[0189] Anti-GFR α 3 antibodies were also isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in U.S. 2007/0280945A1. Using this method, several fully human anti-GFR α 3 antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H4H2207N, H4H2212N, H4H2236N, H4H2243N, H4H2210N, H4H2234N, H4H2291S, H4H2292S, H4H2293P, H4H2294S, H4H2295S, H4H2296S, H4H2341S, H4H2342P, H4H2344S, H4H2345S, H4H2346S, H4H2350P, H4H2352S, H4H2354S, H4H2355S, H4H2357S and H4H2364S.

[0190] The biological properties of the exemplary anti-GFR α 3 antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2. Heavy and Light Chain Variable Region Amino Acid Sequences

[0191] Table 1 sets forth the heavy and light chain variable region amino acid sequence pairs of selected anti-GFR α 3 antibodies and their corresponding antibody identifiers. Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (e.g. "H4H", "H1M", "H2M"), followed by a numerical identifier (e.g. "2207" as shown in Table 1), followed by a "P", "S", or "N" suffix. Thus, according to this nomenclature, an antibody may be referred to as, e.g.

"H4H2207N". The H4H, H1M, and H2M prefixes on the antibody designations used herein indicate the particular Fc region of the antibody. For example, an "H2M" antibody has a mouse IgG2 Fc, whereas an "H4H" antibody has a human IgG4 Fc. As will be appreciated by a person of ordinary skill in the art, an H1M or H2M antibody can be converted to an H4H antibody, and vice versa, but in any event, the variable domains (including the CDRs), which are indicated by the numerical identifiers shown in Table 1, will remain the same. Antibodies having the same numerical antibody designation, but differing by a letter suffix of N, B, S or P refer to antibodies having heavy and light chains with identical CDR sequences but with sequence variations in regions that fall outside of the CDR sequences (*i.e.*, in the framework regions). Thus, N, B, S and P variants of a particular antibody have identical CDR sequences within their heavy and light chain variable regions but differ from one another within their framework regions.

Table 1

Antibody Designation	AMINO ACID SEQ ID NOS:							
	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
H4H2207N	2	4	6	8	10	12	14	16

	AMINO ACID SEQ ID NOS:							
Antibody Designation	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
H4H2212N	18	20	22	24	26	28	30	32
H4H2236N3	34	36	38	40	42	44	46	48
H4H2243N2	50	52	54	56	58	60	62	64
H4H2210N	66	68	70	72	74	76	78	80
H4H2234N	82	84	86	88	90	92	94	96
H4H2291S	98	100	102	104	106	108	110	112
H4H2292S	114	116	118	120	122	124	126	128
H4H2293P	130	132	134	136	138	140	142	144
H4H2294S	146	148	150	152	154	156	158	160
H4H2295S	162	164	166	168	170	172	174	176
H4H2296S	178	180	182	184	186	188	190	192
H4H2341S	194	196	198	200	202	204	206	208
H4H2342P	210	212	214	216	218	220	222	224
H4H2344S	226	228	230	232	234	236	238	240
H4H2345S	242	244	246	248	250	252	254	256
H4H2346S	258	260	262	264	266	268	270	272
H4H2350P	274	276	278	280	282	284	286	288
H4H2352S	290	292	294	296	298	300	302	304
H4H2354S	306	308	310	312	314	316	318	320
H4H2355S	322	324	326	328	330	332	334	336
H4H2357S	338	340	342	344	346	348	350	352
H4H2364S	354	356	358	360	362	364	366	368
H1M2243N	381	383	385	387	389	391	393	395
H1M2236N	397	399	401	403	405	407	409	411

Example 2. Variable Gene Utilization Analysis

[0192] To analyze the structure of antibodies produced, the nucleic acids encoding antibody variable regions were cloned and sequenced. From the nucleic acid sequence and predicted amino acid sequence of the antibodies, gene usage was identified for each Heavy Chain Variable Region (HCVR) and Light Chain Variable Region (LCVR). Table 2 sets forth the gene usage for selected antibodies in accordance with the invention.

Table 2

AbPID	HCVR			LCVR	
	V _H	D _H	J _H	V _K	J _K
H1M2207N	3-9	6-6	4	1-5	2
H1M2212N	3-23	1-26	4	4-1	1
H1M2236N	3-23	3-3	6	1-16	4
H4H2236N3	3-23	3-3	6	1-16	4
H1M2243N	1-18	6-6	6	1-16	3
H4H2243N2	1-18	6-6	6	1-16	3
H2M2210N	3-23	1-20	3	3-20	4
H2M2234N	3-23	5-18	4	4-1	1
H4H2291S	3-23	6-6	6	1D-12	4
H4H2292S	3-33	1-7	3	1-39	3
H4H2293P	3-33	2-15	3	1-39	2
H4H2294S	3-23	6-6	6	1D-12	3
H4H2295S	3-23	6-6	6	1D-12	3
H4H2296S	3-23	6-6	6	1D-12	3
H4H2341S	1-69	3-10	5	1-39	5
H4H2342P	3-23	1-26	4	1-27	3
H4H2344S	3-33	2-15	3	1-39	2
H4H2345S	3-9	1-26	4	1-27	4
H4H2346S	3-33	2-15	3	1-39	2
H4H2350P	4-59	2-21	4	1-9	1
H4H2352S	1-18	3-3	3	3-20	2
H4H2354S	3-33	2-15	3	1-39	2
H4H2355S	3-23	6-6	4	1-5	4
H4H2357S	3-23	3-10	6	1-12	4
H4H2364S	3-23	6-6	6	1D-12	3

Example 3. Binding Affinities of GFR α 3 Antibodies

[0193] Binding associative and dissociative rate constants (k_a and k_d , respectively) and calculated equilibrium dissociation constants and dissociative half-lives (K_D and $t_{1/2}$, respectively) for antigen binding to anti-GFR α 3 antibodies were determined using a real-time surface plasmon resonance biosensor (Biacore T200) assay at 25°C and 37°C. Antibodies were tested for binding to human GFR α 3 expressed with either a C-terminal myc-myc-

hexahistidine tag (hGFR α 3-mmh; SEQ ID: 370, a C-terminal hFc tag (hGFR α 3-hFc; SEQ ID:371), or a C-terminal mFc tag (hGFR α 3-mFc; SEQ ID:372), as well as monkey GFR α 3 expressed with a C-terminal myc-myc-hexahistidine tag (MfGFR α 3-mmh; SEQ ID:373). Anti-GFR α 3 antibodies were captured on either a goat anti-mouse IgG polyclonal antibody (GE Healthcare, # BR-1008-38) or a mouse anti-human IgG monoclonal antibody (GE Healthcare, #BR-1008-39) surface created through direct amine coupling to a Biacore CM5 sensor chip. Kinetic experiments were carried out using HBS-EP (10mM HEPES, 150mM NaCl, 3mM EDTA, 0.05% Surfactant P20, at pH 7.4) or PBS buffer containing 0.05% v/v surfactant P20 as both the running buffer and the sample buffer. Binding to human GFR α 3-mmh or monkey GFR α 3-mmh was evaluated by injecting several concentrations ranging from 200 to 7.4 nM (3-fold dilutions) across the captured antibody surface. Binding to human GFR α 3-mFc or human GFR α 3-hFc was evaluated by injecting several concentrations ranging from 100 to 3.7 nM (3-fold dilutions) across the captured antibody surface. Antibody-antigen association was monitored for up to 4 minutes, while dissociation in buffer was monitored for up to 20 minutes. Kinetic association (k_a) and dissociation (k_d) rate constants were determined by processing and fitting the data to a 1:1 binding model using Scrubber 2.0c curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives ($t_{1/2}$) were calculated from the kinetic rate constants as: K_D (M) = k_d / k_a and $t_{1/2}$ (min) = $[\ln 2 / (60 * k_d)]$.

[0194] As shown in Table 3, at 25°C, all 25 anti-GFR α 3 antibodies bound to hGFR α 3-mmh with K_D values ranging from 82.0pM to 29.7nM. At 37°C, all 25 anti-GFR α 3 antibodies bound to hGFR α 3-mmh with K_D values ranging from 118pM to 47.3nM. As shown in Table 4, at 25°C, all 23 anti-GFR α 3 antibodies bound to MfGFR α 3-mmh with K_D values ranging from 2.90pM to 97.2nM. At 37°C, all 23 anti-GFR α 3 antibodies bound to MfGFR α 3-mmh with K_D values ranging from 11.7pM to 145nM. As shown in Table 5, at 25°C and 37°C, 6 of the 23 anti-GFR α 3 antibodies were tested for binding to hGFR α 3-hFc, while the other 17 antibodies were tested for binding to hGFR α 3-mFc. At 25°C, the 6 anti-GFR α 3 antibodies tested for binding to hGFR α 3-hFc bound with K_D values ranging from 7.50pM to 220pM. At 37°C, the 6 anti-GFR α 3 antibodies tested for binding to hGFR α 3-hFc bound with K_D values ranging from 41.3pM to 531pM. At 25°C, the 17 anti-GFR α 3 antibodies tested for binding to hGFR α 3-mFc bound with K_D values ranging from 0.467pM to 58.4pM. At 37°C, the 17 anti-GFR α 3 antibodies tested for binding to hGFR α 3-mFc bound with K_D values ranging from 13.2pM to 106pM.

Table 3: Kinetics of hGFR α 3-mmH binding to different anti-GFR α 3 antibodies at 25°C and at 37°C

AbPID	25°C				37°C			
	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H2291S	4.18E+05	1.64E-04	3.93E-10	70	5.58E+05	3.23E-04	5.80E-10	36
H4H2292S	1.08E+05	5.19E-05	4.83E-10	223	1.28E+05	2.49E-04	1.94E-09	46

	25°C				37°C			
AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H2293P	5.81E+05	1.27E-04	2.19E-10	91	7.81E+05	2.44E-04	3.13E-10	47
H4H2294S	5.63E+05	7.99E-05	1.42E-10	145	7.73E+05	2.61E-04	3.38E-10	44
H4H2295S	4.75E+05	2.56E-04	5.40E-10	45	6.69E+05	1.19E-03	1.77E-09	10
H4H2296S	5.63E+05	1.87E-04	3.32E-10	62	7.65E+05	6.14E-04	8.02E-10	19
H4H2341S	1.59E+05	2.67E-04	1.68E-09	43	2.48E+05	7.37E-04	2.98E-09	16
H4H2342P	1.86E+05	2.04E-04	1.10E-09	57	3.30E+05	6.71E-04	2.03E-09	17
H4H2344S	1.83E+05	2.40E-04	1.31E-09	48	2.80E+05	7.24E-04	2.58E-09	16
H4H2345S	1.09E+05	3.23E-03	2.97E-08	4	1.84E+05	8.70E-03	4.73E-08	1
H4H2346S	1.86E+05	7.99E-05	4.30E-10	145	4.19E+05	5.89E-04	1.41E-09	20
H4H2350P	1.03E+05	2.07E-04	2.01E-09	56	1.34E+05	1.28E-03	9.61E-09	9
H4H2352S	7.09E+05	5.81E-05	8.20E-11	199	1.18E+06	1.39E-04	1.18E-10	83
H4H2354S	2.00E+05	1.10E-04	5.48E-10	105	2.81E+05	6.49E-04	2.31E-09	18
H4H2355S	1.86E+05	1.52E-04	8.21E-10	76	2.81E+05	1.23E-03	4.37E-09	9
H4H2357S	2.30E+05	5.57E-04	2.42E-09	21	2.95E+05	2.10E-03	7.12E-09	6
H4H2364S	3.53E+05	3.67E-05	1.04E-10	315	3.38E+05	2.73E-04	8.09E-10	42
H1M2207N	5.61E+04	9.00E-04	1.60E-08	13	1.33E+05	1.44E-03	1.08E-08	8
H2aM2210N	6.73E+04	8.63E-04	1.28E-08	13	2.12E+05	3.35E-03	1.58E-08	3
H1M2212N	8.00E+05	1.58E-04	1.97E-10	73	1.02E+06	3.03E-04	2.97E-10	38
H2aM2234N	6.57E+05	7.11E-04	1.08E-09	16	7.93E+05	2.72E-03	3.43E-09	4

	25°C				37°C			
AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H1M2236N	7.60E+05	2.08E-04	2.75E-10	56	1.03E+06	5.50E-04	5.32E-10	21
H4H2236N3	9.22E+05	2.33E-04	2.53E-10	50	1.96E+06	7.48E-04	3.82E-10	15
H4H2243N2	2.67E+05	7.80E-04	2.92E-09	15	4.69E+05	2.44E-03	5.20E-09	5
H1M2243N	1.28E+05	2.61E-04	2.04E-09	44	1.37E+05	5.95E-04	4.35E-09	19

Table 4: Kinetics of MfGFR α 3-mmH binding to different anti-GFR α 3 antibodies at 25°C and at 37°C

	25°C				37°C			
AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H2291S	1.51E+05	2.79E-04	1.85E-09	41	3.57E+05	6.93E-04	1.94E-09	17
H4H2292S	7.76E+04	1.22E-04	1.57E-09	95	8.95E+04	1.95E-04	2.18E-09	59
H4H2293P	2.90E+05	4.17E-05	1.44E-10	277	4.41E+05	1.58E-04	3.58E-10	73
H4H2294S	3.25E+05	2.04E-04	6.27E-10	57	4.33E+05	9.74E-04	2.25E-09	12
H4H2295S	1.83E+05	9.73E-04	5.32E-09	12	2.76E+05	5.61E-03	2.04E-08	2
H4H2296S	1.93E+05	6.51E-04	3.37E-09	18	2.77E+05	2.85E-03	1.03E-08	4
H4H2341S	9.38E+04	1.30E-04	1.39E-09	89	1.44E+05	5.08E-04	3.53E-09	23
H4H2342P	9.37E+04	5.50E-04	5.87E-09	21	1.50E+05	1.66E-03	1.11E-08	7
H4H2344S	1.04E+05	1.15E-04	1.10E-09	101	1.61E+05	5.75E-04	3.57E-09	20
H4H2345S	9.75E+04	2.79E-03	2.87E-08	4	1.34E+05	3.53E-03	2.63E-08	3
H4H2346S	1.08E+05	5.98E-05	5.56E-10	193	1.53E+05	5.11E-04	3.34E-09	23
H4H2350P	6.47E+04	1.11E-04	1.71E-09	104	7.48E+04	8.96E-04	1.20E-08	13
H4H2352S	3.45E+05	1.00E-06	2.90E-12	11550	5.57E+05	6.53E-05	1.17E-10	177

	25°C				37°C			
AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H2354S	1.09E+05	6.23E-05	5.74E-10	185	1.57E+05	4.35E-04	2.78E-09	27
H4H2355S	1.05E+05	6.78E-05	6.49E-10	170	1.73E+05	9.13E-04	5.29E-09	13
H4H2357S	1.40E+05	3.15E-04	2.26E-09	37	1.72E+05	1.35E-03	7.86E-09	9
H4H2364S	1.22E+05	1.30E-04	1.06E-09	89	1.68E+05	8.61E-04	5.14E-09	13
H1M2207N	3.99E+04	3.88E-03	9.72E-08	3	4.58E+04	6.63E-03	1.45E-07	2
H2aM2210N	4.16E+04	1.20E-03	2.89E-08	10	8.09E+04	6.18E-03	7.64E-08	2
H1M2212N	3.84E+05	1.12E-04	2.93E-10	103	8.84E+05	2.60E-04	2.94E-10	44
H2aM2234N	4.27E+05	5.71E-04	1.34E-09	20	4.29E+05	2.11E-03	4.91E-09	5
H1M2236N	2.96E+05	2.86E-04	9.70E-10	40	4.34E+05	1.12E-03	2.58E-09	10
H1M2243N	6.46E+04	6.58E-04	1.02E-08	18	5.02E+04	2.75E-03	5.47E-08	4

Table 5: Kinetics of hGFR α 3-hFc or hGFR α 3-mFc binding to different anti-GFR α 3 antibodies at 25°C and at 37°C

	25°C				37°C			
AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H2291S	1.03E+06	4.78E-06	4.63E-12	2417	1.33E+06	3.84E-05	2.89E-11	301
H4H2292S	5.34E+05	1.00E-06	1.87E-12	11550	5.96E+05	2.57E-05	4.32E-11	449
H4H2293P	1.22E+06	1.93E-06	1.59E-12	5988	1.71E+06	5.13E-05	2.99E-11	225
H4H2294S	1.22E+06	5.63E-06	4.63E-12	2052	1.66E+06	3.46E-05	2.09E-11	334
H4H2295S	1.08E+06	1.69E-06	1.57E-12	6822	1.62E+06	4.88E-05	3.01E-11	237
H4H2296S	1.24E+06	4.17E-06	3.37E-12	2770	1.61E+06	4.74E-05	2.94E-11	244
H4H2341S	5.96E+05	1.00E-06	1.68E-12	11550	9.61E+05	7.58E-05	7.89E-11	152

	25°C				37°C			
AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
H4H2342P	6.61E+05	1.00E-06	1.51E-12	11550	1.21E+06	4.28E-05	3.54E-11	270
H4H2344S	5.79E+05	1.56E-06	2.69E-12	7409	1.01E+06	8.96E-05	8.91E-11	129
H4H2345S	5.16E+05	3.01E-05	5.84E-11	384	7.00E+05	7.44E-05	1.06E-10	155
H4H2346S	6.47E+05	1.44E-05	2.22E-11	803	1.75E+06	1.37E-04	7.81E-11	84
H4H2350P	5.09E+05	2.12E-05	4.16E-11	545	2.56E+06	1.26E-04	4.92E-11	92
H4H2352S	2.14E+06	1.00E-06	4.67E-13	11550	2.28E+06	3.00E-05	1.32E-11	385
H4H2354S	5.80E+05	1.09E-05	1.89E-11	1056	1.02E+06	9.11E-05	8.95E-11	127
H4H2355S	6.11E+05	1.00E-06	1.64E-12	11550	1.10E+06	3.39E-05	3.10E-11	341
H4H2357S	7.79E+05	2.52E-05	3.24E-11	458	1.19E+06	9.40E-05	7.93E-11	123
H4H2364S	7.71E+05	1.00E-06	1.30E-12	11550	1.26E+06	4.14E-05	3.28E-11	279
H1M2207N*	1.59E+05	2.60E-05	1.63E-10	444	2.03E+05	1.08E-04	5.31E-10	107
H2aM2210N*	1.68E+05	3.69E-05	2.20E-10	313	3.16E+05	7.66E-05	2.42E-10	151
H1M2212N*	1.12E+06	1.44E-05	1.28E-11	800	1.49E+06	6.17E-05	4.13E-11	187
H2aM2234N*	9.50E+05	9.60E-05	1.01E-10	120	1.26E+06	1.46E-04	1.16E-10	79
H1M2236N*	1.28E+06	1.76E-05	1.37E-11	658	1.58E+06	9.65E-05	6.10E-11	120
H1M2243N*	1.34E+05	1.00E-06	7.50E-12	11550	1.86E+05	2.18E-05	1.17E-10	529
*Tested for binding to hGFR α 3-hFc, all other antibodies tested for binding to hGFR α 3-mFc								

Example 4. Blocking of Human GFR α 3 Binding to Human ARTEMIN by anti-GFR α 3 Antibodies

[0195] The ability of anti-GFR α 3 antibodies to block human GFR α 3 binding to human ARTEMIN in the presence or absence of co-receptor human RET was determined using two different blocking ELISA formats.

[0196] In the first format, recombinant human ARTEMIN protein with a C-terminal myc-myc-hexahistidine tag (hARTEMIN-mmH; SEQ ID:369) was coated at 2 ug/ml in 96-well microtiter plates in PBS buffer overnight at 4°C and then blocked with a solution of 0.5% (w/v) BSA. A constant amount of human GFR α 3 fused with a C-terminal human Fc tag (hGFR α 3-hFc; SEQ ID:371) at 120 pM was pre-mixed with varying amounts of antibodies, ranging from 0 to ~10 nM in serial dilutions, followed by an 1 hour incubation at room temperature (RT) to allow antibody-hGFR α 3-hFc binding to reach equilibrium. The equilibrated sample solutions were then transferred to the hARTEMIN-mmH-coated plate. After 1 hour of binding, the plate was washed, then the bound hGFR α 3-hFc was detected using HRP-conjugated anti-human IgG Fc specific antibody (Jackson Immunochemical, #109-035-098), and colorimetric signals were developed using a TMB HRP substrate (BD Biosciences, #51-2606KC and #51-2607KC). Absorbance was recorded at 450nm on a Victor X5 plate reader (Perkin Elmer) to determine the amount of free hGFR α 3-hFc in the pre-equilibrated hGFR α 3-hFc-antibody solutions that was able to bind to the plate coated with hARTEMIN-mmH. IC₅₀ values, defined as the concentration of antibody required to reduce the signal from a constant concentration of hGFR α 3-hFc by 50%, were calculated from the data using Prism software from GraphPad. The absorbance measured at the constant amount of 120pM hGFR α 3-hFc in the absence of anti-GFR α 3 antibody is defined as 0% blocking and the absorbance with no added hGFR α 3-hFc is defined as 100% blocking. The observed absorbance in the wells containing the highest antibody concentration was used to calculate the maximum blocking percent shown in the table. The results are summarized in Table 6.

[0197] In the second ELISA format, the plates, samples and data were processed similarly as for the first format except both hARTEMIN-mmH and human RET with a C-terminal 10 histidine tag (hRET-10His; R&D Systems, # 1168-CR/CF) were coated for the blocking ELISA experiment. The 96-well microtiter plates were coated with a mixture of 1.2 ug/ml hARTEMIN-mmH and 6.9 ug/ml hRET-10His proteins in PBS overnight at 4°C and then blocked with a solution of 0.5% (w/v) BSA. A constant amount of biotinylated human GFR α 3 with a C-terminal myc-myc-hexahistidine tag (biotin-hGFR α 3-mmH; SEQ ID:370) at 1nM was pre-mixed with varied amounts of anti-GFR α 3 antibodies, ranging from 0 to ~100 nM in serial dilutions, followed by a 1 hour incubation at RT to allow antibody-biotin-hGFR α 3-mmH binding to reach equilibrium. The equilibrated samples were then transferred to the coated plate. After 1 hour of binding, the plate was washed, then the bound biotin-hGFR α 3-mmH was detected using HRP conjugated streptavidin (Pierce, #N200), and colorimetric signals were developed using TMB HRP substrates. IC₅₀ values and the maximal blocking by each antibody are shown in the Table 6.

[0198] As shown in Table 6, 9 of the 23 anti-GFR α 3 antibodies blocked 51-94% of the hGFR α 3-hFc binding to coated hARTEMIN-mmH with IC₅₀ values ranging from 43.8pM to 723pM in the

first ELISA format. Eight of the 23 anti-GFR α 3 antibodies caused the hGFR α 3-hFc binding signal to increase ("enhancer" in Table 6) at many of the higher tested antibody concentrations in the first ELISA format. Six of the 23 antibodies tested in the first ELISA format did not block or enhance the hGFR α 3-hFc binding signal to coated hARTEMIN-mmH. As shown in Table 6, for the second ELISA format, 17 of the 23 anti-GFR α 3 antibodies blocked 75-100% of the biotin-hGFR α 3-mmH binding to dual-coated hARTEMIN-mmH and hRET-10His with IC₅₀ values ranging from 403pM to 14.6nM. Also in the second ELISA format, five of the 23 anti-GFR α 3 antibodies caused the biotin-hGFR α 3-mmH binding signal to increase at lower antibody concentrations but blocked 28-95% of the biotin-hGFR α 3-mmH binding to hARTEMIN-mmH and hRET-10His at antibody concentrations 1nM and above ("enhancer" in Table 6). One anti-GFR α 3 antibody caused the biotin-hGFR α 3-mmH binding signal to increase ("enhancer" in Table 6) at the higher tested antibody concentrations, with no blocking at any concentration, in the second ELISA format.

Table 6: ELISA Blocking of human GFR α 3 to human ARTEMIN alone or human ARTEMIN and human RET

	ELISA format 1: Ab blocking 120pM hGFRα3-hFc binding to coated hARTEMIN-mmH		ELISA format 2: Ab blocking 1nM biotin-hGFRα3-mmH binding to coated hARTEMIN-mmH and hRET-10His	
AbPID	IC ₅₀ (M)	% max blocking	IC ₅₀ (M)	% max blocking
H4H2207N	enhancer	NB	7.30E-09	85
H4H2210N	enhancer	NB	enhancer	NB
H4H2212N	4.38E-11	81	4.03E-10	99
H4H2234N	8.29E-11	70	3.42E-09	97
H4H2236N3	enhancer	NB	enhancer	68
H4H2243N2	enhancer	NB	1.12E-09	95
H4H2291S	NB	NB	enhancer	28
H4H2292S	7.23E-10	89	1.76E-09	100
H4H2293P	2.60E-10	93	7.38E-09	95
H4H2294S	NB	NB	9.52E-10	95
H4H2295S	enhancer	NB	enhancer	44
H4H2296S	NB	NB	enhancer	91
H4H2341S	enhancer	NB	1.62E-09	98
H4H2342P	enhancer	NB	1.08E-09	97
H4H2344S	1.33E-10	94	4.59E-10	100
H4H2345S	enhancer	NB	1.46E-08	75
H4H2346S	9.78E-11	92	7.971E-10	99
H4H2350P	4.96E-10	93	1.29E-09	91

	ELISA format 1: Ab blocking 120pM hGFR α 3-hFc binding to coated hARTEMIN-mmH		ELISA format 2: Ab blocking 1nM biotin-hGFR α 3-mmH binding to coated hARTEMIN-mmH and hRET-10His	
AbPID	IC ₅₀ (M)	% max blocking	IC ₅₀ (M)	% max blocking
H4H2352S	6.58E-11	51	7.61E-10	100
H4H2354S	1.16E-10	92	1.32E-09	97
H4H2355S	NB	NB	enhancer	95
H4H2357S	NB	NB	3.28E-09	86
H4H2364S	NB	NB	1.45E-09	100
NB = non-blocker				

Example 5. Measuring the Ability of Anti-GFR α 3 Antibodies to Block Activation of GFR α 3 and RET by the Ligand ARTEMIN *in vitro*

[0199] The ability of anti-GFR α 3 antibodies to block activation of GFR α 3 and RET by its ligand ARTEMIN *in vitro* was determined using a cell-based assay. HEK293 cells modified to stably express both human GFR α 3 (amino acids 1-400 of accession number NP_001487.2) and human RET (amino acids 1-1072 of accession number NP_065681) were generated and then transduced with a SRE responsive luciferase reporter (SRE-luc; Sabiosciences, CCS-010L) (HEK293/hGFR α 3/hRET cells).

[0200] Twenty thousand HEK293/hGFR α 3/hRET/SRE-luc cells were seeded into Poly D-Lysine coated 96 well plates (Greiner, #35-4620) in Optimem (GIBCO, #31985) containing 0.5% FBS and then grown overnight in 5% CO₂ at 37°C. The cells were then incubated for 1 hour at room temperature with serial dilutions of anti-GFR α 3 antibodies ranging from 5pM to 300nM. A constant dose (100pM) of human ARTEMIN expressed with a C-terminal myc myc hexahistidine tag (SEQ ID:369) was then added to the cells and incubated for an additional 6 hours. Luciferase activity was measured as relative light units (RLU) on a Victor luminometer (Perkin Elmer) after the addition of OneGlo reagent (Promega, #E6051). EC₅₀ and IC₅₀ values were calculated from a four-parameter logistic equation over a 12-point response curve using GraphPad Prism data analysis software.

[0201] Twenty-three anti-GFR α 3 antibodies were tested for their ability to inhibit ARTEMIN-dependent activation of the HEK293/hGFR α 3/hRET/SRE-luc cells. As shown in Table 7, all 23 antibodies tested blocked luciferase activity with IC₅₀ values ranging from 0.2nM to 48.3nM, and 19 of 23 antibodies blocked to the baseline at a concentration of 300nM. Four of the 23 antibodies (H4H2344S, H4H2345S, H4H2346S, and H4H2354S-1) did not block to baseline at any of the antibody concentrations tested.

Table 7: Inhibition of ARTEMIN-dependent stimulation of HEK293/hGFR α 3/hRET/SRE-luc cells by anti-GFR α 3 antibodies

AbPID	IC ₅₀ (nM)
H4H2294S	0.27
H4H2342P	1.0
H4H2212N	0.80
H4H2292S	4.6
H4H2243N2	0.30
H4H2352S	0.92
H4H2207N	2.4
H4H2210N	2.9
H4H2234N	2.3
H4H2236N3	1.5
H4H2291S	1.3
H4H2293P	20
H4H2294S	1.7
H4H2295S	1.5
H4H2296S	1.4
H4H2341S	7.1
H4H2344S	48
H4H2345S	26
H4H2346S	26
H4H2354S	22
H4H2355S	2.3
H4H2357S	4.9
H4H2364S	2.3

Example 6. Inhibition of ARTEMIN-sensitized capsaicin thermal hyperalgesia

[0202] To induce ARTEMIN-sensitized thermal hyperalgesia in mice, each mouse was pretreated with an intra-plantar injection of 0.5 micrograms mouse recombinant ARTEMIN (R&D Systems, #1085-AR) 24 hours before administering an intra-plantar injection of 0.5 micrograms capsaicin (a sub-optimal dose) from a 100 mM solution in DMSO (Sigma-Aldrich, #M-2028). Thermal hyperalgesia was evaluated using the Hargreaves' Test, in which a beam of light is directed at the injected paw until the animal withdraws its paw. The latency to withdraw is recorded as a behavioral measure of nociception. Thermal hyperalgesia is consistently

ARTEMIN-sensitized at 3 days after capsaicin administration based on significantly decreased paw withdrawal latencies. For these studies, a baseline value for withdrawal latency was measured before dosing with either ARTEMIN or capsaicin followed by a second measurement three days after capsaicin treatment. The experimenter conducting these assays was blind to the treatment group of the animals.

[0203] For all experiments evaluating the efficacy of human anti-GFR α 3 antibodies in ARTEMIN-sensitized hyperalgesia, adult mice homozygous for the expression of human GFR α 3 in place of mouse GFR α 3 ("humanized GFR α 3") were used. Both male and female mice were used in each assay, with sex balanced across treatment groups (a total of 8 mice per treatment or control group). Humanized GFR α 3 mice were previously determined to have ARTEMIN-induced capsaicin thermal hyperalgesia latency responses similar to those observed in wild-type mice.

[0204] Six anti-GFR α 3 antibodies (H4H2212N, H4H2243N2, H4H2292S, H4H2294S, H4H2342P, and H4H2352S-1) were tested in the model. All antibodies were diluted in phosphate-buffered saline (PBS) and were administered subcutaneously at 25mg/kg in a 1ml/100g body weight volume 24 hours prior to ARTEMIN injection into the hindpaw. In each experiment, one group of animals received an isotype control antibody.

[0205] Pain sensitivity for each treatment or control group was defined as percentage of baseline withdrawal latency (%BWL), calculated as the fractional change for each animal's time-based withdrawal latency (WL) three days after capsaicin treatment compared to their baseline withdrawal latency without capsaicin treatment:

$$\%BWL = [(WL_{\text{(capsaicin)}} - WL_{\text{(no capsaicin)}}) / WL_{\text{(no capsaicin)}}] \times 100$$

[0206] Using %BWL, larger negative values indicate greater thermal hyperalgesia.

[0207] Table 8 shows the summary of group means (in boldface type) and standard error of the means (in italics) for percentage of baseline withdrawal latency (%BWL) in the ARTEMIN-sensitized capsaicin thermal hyperalgesia model assessed at three days after capsaicin injection.

[0208] As shown in Table 8, mice treated with anti-hGFR α 3 antibodies exhibited increases in %BWL (smaller negative or positive values) compared to mice treated with the isotype control antibody. Four antibodies, H4H2352S, H4H2243N2, H4H2294S, and H4H2342P promoted the greatest resistance to thermal hyperalgesia across all experiments performed.

Table 8: Data Summary in the ARTEMIN-sensitized capsaicin thermal hyperalgesia model assessed at three days after capsaicin injection.

AbPID	%BWL			
	Exp. 323	Exp. 361	Exp. 367	Exp. 380
Isotype control	-17 ± 7.6	-32 ± 6.8	-40 ± 4.8	-35 ± 3.5
H4H2292S	0.72 ± 19	<i>nd</i>	<i>nd</i>	-26 ± 5.9

AbPID	%BWL			
	Exp. 323	Exp. 361	Exp. 367	Exp. 380
H4H2352S	27 ± 15	nd	-5.6 ± 9.4**	nd
H4H2243N2	20 ± 18	nd	nd	21 ± 6.4***
H4H2294S	nd	-9.0 ± 12	2.3 ± 12**	nd
H4H2342P	nd	-12 ± 9.3	18 ± 8.3***	nd
H4H2212N	nd	-22 ± 6.9	nd	nd
significantly different than isotype control, **p<.01; ***p<.001 (nd=not tested in this experiment)				

Example 7. Testing of anti-GFRα3 Antibodies for Cross-Reactivity with GFRα1 and GFRα2

[0209] The ability of anti-GFRα3 antibodies to bind to GDNF-family receptors was assessed using an Octet Red biosensor (Fortebio, Inc.). Antibodies were tested for binding to either human GFRα1 expressed with a C-terminal human Fc tag and a hexahistidine tag (hGFRα1-hFc-6His, R&D Systems # 714-GR), human GFRα1 expressed with only a C-terminal human Fc tag (hGFRα1-hFc; SEQ ID: 376), human GFRα2 expressed with a C-terminal human Fc tag and a hexahistidine tag (hGFRα2-hFc-6His, R&D Systems #613-FR), human GFRα3 expressed with a C-terminal human Fc tag (hGFRα3-hFc, SEQ ID:371), or an irrelevant human Fc tagged protein. Antigens were captured onto anti-human Fc sensor tips from 10ug/mL solutions for 5 minutes. The coated sensor tips were then blocked with a 100ug/mL solution of irrelevant human Fc antibodies for 5 minutes. Blocked sensor tips were then submerged into wells containing 667uM of each anti-GFRα3 antibody or buffer alone for 10 minutes. The experiment was performed at 25°C with a flow rate of 1000 rpm using HBST+BSA buffer (10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05% w/v Surfactant P20, 0.1 mg/mL BSA, pH 7.4). The binding response (measured in units of nm) at each step of the experiment was monitored and recorded.

[0210] All six of the tested anti-GFRα3 antibodies showed binding above 1.0 nm to the hGFRα3-hFc protein, but did not demonstrate any measurable binding to the other GDNF-family receptors or to the irrelevant human Fc tagged protein, as shown in Table 9.

Table 9. Reactivity of Anti-GFRα3 Antibodies with GFRα1, GFRα2 and GFRα3

Antigen	Capture Level (nm) +/- Std dev	100 ug/mL H4H229 4S Bound (nm)	100 ug/mL H4H2342 P Bound (nm)	100 ug/mL H4H224 3N2 Bound (nm)	100 ug/mL H4H221 2N Bound (nm)	100 ug/mL H4H235 2S Bound (nm)	100 ug/mL H4H229 2S Bound (nm)	Buffer
hGFR α 1-hFc	1.89 $\pm$ 0.14	0.04	0.06	0.03	0.00	0.02	0.05	-0.07
hGFR α 1-hFc-6his	1.66 $\pm$ 0.10	0.03	0.08	0.03	-0.01	0.03	0.03	-0.07
hGFR α 2-hFc-6his	1.49 $\pm$ 0.09	0.06	0.12	0.06	0.02	0.04	0.05	-0.06
hGFR α 3-hFc	1.68 $\pm$ 0.10	1.17	1.59	1.11	1.18	1.25	1.04	-0.09
Irrelevant hFc tagged protein	1.00 $\pm$ 0.06	0.03	0.07	0.03	0.00	0.03	0.02	-0.08

Example 8. Measuring the Ability of Anti-GFR α 3 antibodies to block ARTEMIN stimulation in a HEK293/MfGFR α 3/MfRet/SRE-Luc bioassay

[0211] The ability of anti-GFR α 3 antibodies to block activation of cynomolgus GFR α 3 and cynomolgus RET by its ligand ARTEMIN *in vitro* was determined using a cell-based assay. HEK293 cells modified to stably express both cynomolgus GFR α 3 (MfGFR α 3; SEQ ID: 377) and cynomolgus RET (MfRET; SEQ ID: 378) were generated and then transduced with a Signal Lenti SRE Reporter (SA Biosciences, #CLS-010L) expressing the firefly luciferase gene under the control of a minimal CMV promoter and tandem repeats of the serum response element to generate the HEK293/MfGFR α 3/MfRet/SRE-Luc cell line.

[0212] For the bioassay, 20,000 HEK293/MfGFR α 3/MfRet/SRE-Luc cells were seeded onto Poly D-Lysine coated 96 well plates (Greiner, #35-4620) in Optimem (GIBCO, #31985) containing 0.5% FBS and then grown overnight at 5% CO₂ at 37°C. The cells were then incubated for 1 hour with serial dilutions of anti-GFR α 3 antibodies ranging from 5pM to 300nM. A constant dose (500pM) of human ARTEMIN expressed with a C-terminal myc-myc-hexahistidine tag (Human ARTEMIN-MMH; SEQ ID: 369) was then added to the cells and incubated for an additional 6 hours. To determine the EC₅₀ value of human ARTEMIN-MMH from dose response curves, serial dilutions of human ARTEMIN-MMH ranging from 0.5 pM to 10nM was added to the cells without antibodies and incubated for 6 hours at 37°C. Luciferase activity was measured as relative light units (RLU) on a Victor luminometer (Perkin Elmer) after the addition of OneGlo reagent (Promega, #E6051). EC₅₀ and IC₅₀ values were calculated from a four-parameter logistic equation over a 12-point response curve using GraphPad Prism data

analysis software.

[0213] Six anti-GFR α 3 antibodies were tested for their ability to inhibit ARTEMIN-dependent activation of the HEK293/MfGFR α 3/MfRET/SRE-luc cells. As shown in Table 10, all six antibodies tested completely blocked luciferase activity with IC₅₀ values ranging from 0.7nM to 2.5nM. Human ARTEMIN-MMH stimulated SRE-dependent luciferase activity in the HEK293/mfGFR α 3/mfRet/SRE-LUC cell line with an EC₅₀ value of 70pM.

Table 10: Inhibition of ARTEMIN-dependent stimulation of HEK293/MfGFR α 3/MfRET/SRE-luc cells by anti-GFR α 3 antibodies

Antibody	IC ₅₀ (nM)
H4H2294S	0.7
H4H2342P	2.5
H4H2212N	1.8
H4H2292S	1.5
H4H2243N2	0.8
H4H2352S	1.3

Example 9. Generation of a Bi-specific Anti-GFR α 3 Antibody

[0214] Various bi-specific antibodies are generated for use in practicing the methods described herein. For example, GFR α 3-specific antibodies are generated in a bi-specific format (a "bi-specific") in which variable regions binding to distinct epitopes on GFR α 3 are linked together to confer dual-epitope specificity within a single binding molecule. Appropriately designed bi-specifics may enhance overall GFR α 3 blocking efficacy through increasing both GFR α 3 specificity and binding avidity. Variable regions with specificity for individual different epitopes within any of the three cysteine repeats or that can bind to different regions within one epitope of any of the three cysteine repeats are paired on a structural scaffold that allows each variable region to bind simultaneously to the separate epitopes, or to different regions within one epitope. In one example for a bi-specific, heavy chain variable regions (V_H) from a binder with specificity for one epitope within one cysteine repeat are recombined with light chain variable regions (V_L) from a series of binders having specificity for a second epitope within any of the other two cysteine repeats to identify non-cognate V_L partners that can be paired with an original V_H without disrupting the original specificity for that V_H. In this way, a single V_L segment (e.g., V_{L1}) can be combined with two different V_H domains (e.g., V_{H1} and V_{H2}) to generate a bi-specific comprised of two binding "arms" (V_{H1}- V_{L1} and V_{H2}- V_{L1}). Use of a single V_L segment reduces the complexity of the system and thereby simplifies and increases efficiency in cloning, expression, and purification processes used to generate the bi-specific (See, for example, USSN13/022759 and US2010/0331527).

[0215] Alternatively, antibodies that bind both GFR α 3 and a second target, such as, but not limited to, for example, RET may be prepared in a bi-specific format using techniques described herein, or other techniques known to those skilled in the art. Antibody variable regions binding to distinct GFR α 3 regions that are extracellularly exposed are linked together with variable regions that bind to relevant sites on, for example, the ligand, artemin, other GFR α receptors, or to RET, to confer dual-antigen specificity within a single binding molecule. Variable regions with specificity for individual epitopes of GFR α 3, are combined with a variable region with specificity for, for example, artemin and are paired on a structural scaffold that allows each variable region to bind to the separate antigens.

[0216] The bi-specific binders are tested for binding and functional blocking of the target antigens, for example, GFR α 3 and/or artemin, other GFR α receptors, or RET, in any of the assays described above for antibodies. For example, standard methods to measure soluble protein binding are used to assess the bispecific interaction with its antigen(s), such as Biacore, ELISA, size exclusion chromatography, multi-angle laser light scattering, direct scanning calorimetry, and other methods. Binding of bi-specific antibodies to cells expressing GFR α 3 is determined through flow cytometry using a fluorescently labeled secondary antibody recognizing the target antigen on the cells. Binding experiments with peptides can also be conducted using surface plasmon resonance experiments, in which real-time binding interaction of peptide to antibody is measured by flowing a peptide or bi-specific across a sensor surface on which bi-specific or peptide, respectively, is captured. Functional *in vitro* blocking of the GFR α 3 receptor by a bi-specific is determined using any bioassay such as that described herein, or by *in vivo* determination of reaction to pain in appropriate animal models, such as those described herein. Functional *in vitro* blocking of GFR α 3 or its ligand, artemin, by a bi-specific is determined using any bioassay such as that described in WO2010/077854, or in US2010/0166768, or by *in vivo* determination of hypersensitivity to thermal stimuli in appropriate animal models, such as those described herein.

Example 10. Surface plasmon resonance derived binding affinities and kinetic constants of monoclonal anti-mouse GFR α 3 antibodies

[0217] Binding associative and dissociative rate constants (k_a and k_d , respectively) and calculated equilibrium dissociation constants and dissociative half-lives (K_D and $t_{1/2}$, respectively) for antigen binding to anti-mouse GFR α 3 antibodies were determined using a real-time surface plasmon resonance biosensor (Biacore 3000) assay at 25°C. Antibodies were tested for binding to mouse GFR α 3 expressed with myc-myc-hexahistidine tag (mGFR α 3-MMH; SEQ ID: 379,). Anti-mouse GFR α 3 antibodies were captured on a goat anti-mouse IgG polyclonal antibody (GE Healthcare, # BR-1008-38) surface created through direct amine coupling to a Biacore CM5 sensor chip. Kinetic experiments were carried out using HBS-EP (10mM HEPES, 150mM NaCl, 3mM EDTA, 0.05% Surfactant P20, at pH 7.4) as both the running buffer and the sample buffer. Binding to mouse GFR α 3-MMH was evaluated by injecting several concentrations ranging from 100nM to 6.25 nM (2-fold dilutions) across the captured antibody surface. Antibody-antigen association was monitored for up to 5 minutes,

while dissociation in buffer was monitored for up to 10 minutes. Kinetic association (k_a) and dissociation (k_d) rate constants were determined by processing and fitting the data to a 1:1 binding model using Scrubber 2.0c curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives ($t_{1/2}$) were calculated from the kinetic rate constants as: K_D (M) = k_d / k_a and $t_{1/2}$ (min) = $[\ln 2 / (60 * k_d)]$.

[0218] As shown in Table 11, the two anti-mouse GFR α 3 antibodies tested, M1M6986N and M1M6977N, bound to mGFR α 3-MMH at 25°C with K_D values of 23.1pM and 107pM, respectively.

Table 11: Kinetics of mGFR α 3-MMH binding to different anti-mouse GFR α 3 antibodies at 25°C

AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	$t_{1/2}$ (min)
M1M6986N	1.02E+06	2.35E-05	2.31E-11	491
M1M6977N	3.84E+05	4.1E-05	1.07E-10	282

Example 11. Mouse GFR α 3 Blocking ELISA

[0219] The ability of anti-mouse GFR α 3 antibodies to block mouse GFR α 3 binding to mouse ARTEMIS in the presence or absence of co-receptor mouse RET was determined using two different blocking ELISA formats. In the first format, recombinant mouse ARTEMIS (R&D cat# 1085-AR/CF) protein was coated at 2ug/mL (166nM) in 96-well microtiter plates in PBS buffer overnight at 4°C and then blocked with a solution of 0.5% (w/v) BSA. A constant amount (3.5nM) of biotinylated mouse GFR α 3 with a C-terminal myc-myc-hexahistidine tag (Biotin-mGFR α 3-MMH, SEQ ID:379) was pre-mixed with varying amounts of antibodies, ranging from 100nM to 1.6 pM in serial dilutions, followed by 1 hour incubation at room temperature (RT) to allow antibody-biotin-mGFR α 3-MMH binding to reach equilibrium. The equilibrated sample solutions were then transferred to the mARTEMIS-coated plate. After 1 hour of binding, the plate was washed, then the bound biotin-mGFR α 3-MMH was detected using Streptavidin-HRP (Pierce, #N200) and colorimetric signals were developed using a TMB HRP substrate (BD Biosciences, #51-2606KC and #51-2607KC). Absorbance was recorded at 450nm on a Victor X5 plate reader (Perkin Elmer) to determine the amount of free biotin-mGFR α 3-MMH in the pre-equilibrated biotin-mGFR α 3-MMH-antibody solutions that was able to bind to the plate-coated mARTEMIS. IC₅₀ values, defined as the concentration of antibody required to reduce the signal from a constant concentration of biotin-mGFR α 3-MMH by 50%, were calculated from the data using Prism software from GraphPad. The absorbance measured at the constant amount of biotin-mGFR α 3-MMH in the absence of anti-mouse GFR α 3 antibody is defined as 0% blocking and the absorbance with no added biotin-mGFR α 3-MMH is defined as 100% blocking. The observed absorbance in the wells containing the highest antibody concentration was used to calculate the maximum blocking percent shown in the table. The results are summarized in Table 12.

[0220] In the second ELISA format, the plates, samples and data were processed similarly as for the first format except both mouse RET expressed with C-terminal hFc and hexahistidine tags (mRET-hFc-6His; R&D cat# 482-RT/CF) and mARTEMIN (R&D cat# 1085-AR/CF) were coated for the blocking ELISA experiment. The 96-well microtiter plates were coated with a mixture of 1.2ug/mL (100nM) mARTEMIN and 9.5ug/mL (100nM) mRET-hFc-6His proteins in PBS overnight at 4°C and then blocked with a solution of 0.5% (w/v) BSA. A constant amount (350pM) of biotin-mGFR α 3-MMH was pre-mixed with varied amounts of anti-mouse GFR α 3 antibodies, ranging from 100nM to 1.6pM in serial dilutions, followed by a 1 hour incubation at RT to allow antibody- biotin-mGFR α 3-MMH binding to reach equilibrium. The equilibrated samples were then transferred to the coated plate. After 1 hour of binding, the plate was washed, then the bound biotin-mGFR α 3-MMH was detected using HRP conjugated streptavidin and colorimetric signals were developed using TMB HRP substrates. IC₅₀ values and the maximal blocking by each antibody are shown in the Table 12.

[0221] As shown in Table 12, only one anti-mouse GFR α 3 antibody tested, M1M6986N, demonstrated the ability to block biotin-mGFR α 3-MMH from binding to the coated mARTEMIN plate with an IC₅₀ value of 69.1pM. The other anti-mouse GFR α 3 antibody tested, M1M6977N, did not demonstrate any measurable blockade in this ELISA format. Both anti-mouse GFR α 3 antibodies tested, M1M6986N and M1M6977N, demonstrated the ability to completely block biotin-mGFR α 3-MMH from binding to the plates coated with both mARTEMIN and mRET-hFc-6His, with IC₅₀ values of 47.2pM and 366pM, respectively.

Table 12: ELISA Blocking of mouse GFR α 3 to mouse ARTEMIN alone or mouse ARTEMIN and mouse RET

AbPID	ELISA format 1: Antibody blocking 3.5nM biotin-mGFR α 3-MMH binding to coated mARTEMIN		ELISA format 2: Antibody blocking 350pM biotin-mGFR α 3-MMH binding to coated mARTEMIN and mRET-hFc-6His	
	IC ₅₀ (M)	% max blocking	IC ₅₀ (M)	% max blocking
M1M6986N	6.91E-11	100%	4.72E-11	100%
M1M6977N	NB		3.66E-10	100%
NB = non-blocker				

Example 12. Cell based Luciferase bioassay

[0222] The ability of anti-mouse GFR α 3 antibodies to block activation of mouse GFR α 3 and mouse RET by its ligand mouse ARTEMIN *in vitro* was determined using a cell-based assay. HEK293 cells modified to stably express both mouse GFR α 3 (amino acids 1-397 of accession number AAH66202.1) and mouse RET (amino acids 1-1115 of accession number NP_033076.2) were generated and then transduced with a SRE responsive luciferase reporter (SRE-luc; Sabiosciences, CCS-010L) (293/mGFR α 3/mRET/SRE-luc cells).

[0223] Twenty thousand 293/mGFR α 3/mRET/SRE-luc cells were seeded into Poly D-Lysine coated 96 well plates (Greiner, #35-4620) in Optimem (GIBCO, #31985) containing 0.5% FBS and then grown overnight in 5% CO₂ at 37°C. The cells were then incubated for 1 hour at room temperature with serial dilutions of anti-mouse GFR α 3 antibodies ranging from 3 nM to 44 nM. A constant dose (100 pM) of mouse ARTEMIN (R&D, # 1085-AR/CF) was then added to the cells and incubated for an additional 6 hours. Luciferase activity was measured as relative light units (RLU) on a Victor luminometer (Perkin Elmer) after the addition of OneGlo reagent (Promega, #E6051). EC₅₀ and IC₅₀ values were calculated from a four-parameter logistic equation over a 12-point response curve using GraphPad Prism data analysis software.

[0224] As shown in Table 13, both anti-mouse GFR α 3 antibodies tested, M1M6986N and M1M6977N demonstrated the ability to inhibit mouse ARTEMIN-dependent stimulation of 293/mGFR α 3/mRET/SRE-luc cells with IC₅₀ values of approximately 44nM and 3nM, respectively.

Table 13: Inhibition of ARTEMIN-dependent stimulation of 293/mGFR α 3/mRET/SRE-luc cells by anti-mouse GFR α 3 antibodies

Antibody	IC ₅₀ (nM)
M1M6986N	44 $\pm$ 3 (n=2)
M1M6977N	3 $\pm$ 1 (n=3)

Examples 13, 14 and 15: The effect of anti-mouse GFR α 3 antibodies in animal models of bone cancer pain and osteoarthritic pain

[0225] The antibodies described herein are high affinity human antibodies to the GPI-linked alpha receptor for artemin, GFR α 3. Since these antibodies to human GFR α 3 do not cross-react with mouse GFR α 3, *in vivo* assays with these antibodies can only be conducted in mice genetically altered to replace the mouse GFR α 3 sequence with that of human GFR α 3. Initial *in vivo* experiments in these GFR α 3^{hu/hu} mice using pharmacological inhibition of artemin-sensitized capsaicin revealed efficacy of four human antibodies in this *in vivo* assay. In order to expedite the generation of efficacy data, mouse GFR α 3 antibodies were generated to serve as surrogates to the human antibodies. Mice of a mixed C57BL6/129Sv strain that were homozygous for deletion of the endogenous GFR α 3 gene were immunized with recombinant mouse GFR α 3 extracellular domain expressed in Chinese hamster ovary cells. A specific immune response to GFR α 3 was confirmed by immunoassays of serum from the immunized mice. Spleens were collected from mice exhibiting a high specific immune response, and antibody-producing hybridoma cells were generated by fusion of the isolated splenocytes with mouse myeloma cells following standard hybridoma procedures. Hybridoma supernatants were further screened in immunoassays for binding to GFR α 3 and for their ability to block binding of GFR α 3 to either artemin or artemin/Ret coated on a solid surface in an immunoassay format. Supernatants were also screened for their ability to block artemin stimulation of the GFR α 3/Ret

co-receptor pathway in a cell-based bioassay. Variable-region antibody sequences were obtained by PCR amplification of selected hybridoma clones whose antibody proteins exhibited potent blocking in the cell-based assay, and these sequences were used to produce full-length recombinant anti-mouse GFR α 3 antibodies with a mouse IgG1 isotype. Two antibodies were selected for *in vivo* testing that potentially inhibited artemin signaling in the cell-based assay. In the *in vitro* binding immunoassay, antibody M1M6986N blocked binding of GFR α 3 to both artemin or artemin/Ret coated on a solid surface and is referred to here as a direct blocker. Antibody M1M6977N blocked binding of GFR α 3 to coated artemin/Ret but not to artemin alone in the *in vitro* immunoassay and is referred to here as an indirect blocker. These two mouse antibodies, M1M6986N and M1M6977N, were selected for testing in the artemin-sensitized capsaicin thermal analgesia model (described in Example 6), since these two antibodies demonstrated similar binding and blocking profiles to the efficacious human antibodies. These two antibodies were screened for their ability to block artemin-induced sensitization of hyperalgesia *in vivo* in wild type mice. Like their human antibody counterparts, both antibodies significantly inhibited artemin's sensitizing effect on capsaicin thermal hyperalgesia three days after capsaicin injection (Figure 1).

Example 13: Fibrosarcoma Model of Bone Cancer Pain Methodology

Subjects

[0226] Adult male mice on a C57Bl6 background strain were used for two fibrosarcoma experiments at approximately 12 weeks of age. The experimenters measuring outcome data for this experiment were blind to treatment group of the animals throughout data collection, compilation, and analysis.

Bone Cancer Model

[0227] To induce bone cancer pain, the mice were anesthetized and then injected intrafemorally with 1.0×10^6 MC57G fibrosarcoma cells. These cells are derived from a C57Bl/6 mouse fibrosarcoma tumor line. Tumors typically grow aggressively in this model, such that bone destruction is evident by 14 days after tumor implantation. Radiographs were taken at days 7, and 10, and 14 after implantation to verify tumor growth and bone destruction. Bone destruction was scored on a three-point scale such that 0 represented no destruction and 3 represented complete destruction of the femur in the region of the tumor.

Antibody Treatment

[0228] Each animal received 30mg/kg s.c. antibody injections administered the day before

cancer cell implantation and again on day 7. Animals were pseudo-randomly assigned to one of two or three treatment groups: 1) M2M180N isotype (negative) control antibody in two separate experiments, 2) M1M6977N anti-mouse GFR α 3 antibody in two separate experiments or 3) M1M6986N anti-mouse GFR α 3 antibody in the second experiment only. M1M6986 blocks artemin's interaction with GFR α 3, and is thereby considered a "direct" blocker of artemin's action. In contrast, M1M6977N inhibits artemin's action through the GFR α 3/RET complex, and is therefore considered an "indirect" inhibitor.

Measures of Nociception

[0229] Nociceptive responses to the bone tumor were measured using the von Frey Hair test for evoked mechanical (tactile) allodynia, the dynamic weight bearing (DWB) test for willingness to bear weight on a limb, and guarding behavior. Von Frey test results are expressed as grams of pressure required for paw withdrawal. Weight bearing results are expressed as percent body weight placed on the ipsilateral limb. Guarding behavior is expressed as time spent guarding the limb over a two-minute period.

Results

Bone Destruction

[0230] There was no significant effect of antibody treatment on bone destruction score in either experiment suggesting that the antibody treatment had no impact on the severity of the bone cancer itself (data not shown).

Nociceptive Behavior

[0231] There was a statistically significant decrease in tactile allodynia with GFR α 3 antibody treatment after fibrosarcoma injection in the first experiment ($F(1,20)=9.189$, $p=.007$, Figure 2A) and a statistical trend toward efficacy overall in the second experiment ($F(2,29)=3.069$, $p<.062$, Figure 2B), with individual comparisons sometimes achieving significance in the second study (Figure 2B).

[0232] There was no statistically significant effect of GFR α 3 antibodies on dynamic weight bearing on the ipsilateral limb measured 14 days after implantation of bone with fibrosarcoma cells in either experiment, although the first experiment revealed a statistical trend toward efficacy with M1M6977N treatment ($t(10)=2.047$, $p=.068$, Figure 3A; $F(2,28)=1.598$, $p=.220$, Figure 3B).

[0233] GFR α 3 antibodies significantly reduced limb guarding after bone cancer implantation in both fibrosarcoma experiments ($F(1,20)=12.270$, $p=.002$, Figure 4A; $F(2,29)=3.576$, $p=.041$, Figure 4B).

Conclusion

[0234] Treatment with anti-mouse GFR α 3 antibodies significantly reduced nociceptive behaviors in this bone cancer pain model as measured by evaluation of guarding and the von Frey Test of tactile allodynia. In addition, there was a statistical trend toward efficacy of the M1M6977N antibody in weight bearing differential in one experiment. Bone destruction scores were not different in groups receiving anti-mouse GFR α 3 antibodies, suggesting that differences in pain-related measures could not be accounted for by differences in cancer severity. Therefore, our data suggest that neutralizing antibodies against GFR α 3 could be efficacious against bone cancer pain. Because sarcoma cells are more often primary tumors than metastases in bone, and because most bone cancers derive from metastases of primary tumors from other sites, these antibodies were also tested in a model of breast (mammary) carcinoma-induced bone cancer pain. Breast and prostate tumors are among the most common tumors found to metastasize to bone.

Example 14: Breast Carcinoma Model of Bone Cancer Pain Methodology

Subjects

[0235] Adult male mice on a Balb/c background strain were used for a mammary carcinoma bone cancer experiment at approximately 12 weeks of age. The experimenters measuring outcome data for this experiment were blind to treatment group of the animals throughout data collection, compilation, and analysis.

Bone Cancer Model

[0236] To induce bone cancer pain, the mice were anesthetized and then injected intrafemorally with 10,000 4T-1 mammary carcinoma cells. These cells are derived from a Balb/c mammary carcinoma tumor line. Tumors typically grow aggressively in this model, such that tumors are severe by 18 days after implantation. Radiographs were taken at days 10, 14, and 19 after implantation to verify tumor growth and bone destruction. Bone destruction was scored on a three-point scale such that 0 represented no destruction and 3 represented complete destruction of the femur in the region of the tumor.

Antibody Treatment

[0237] Each animal received 30mg/kg s.c. antibody injections administered the day before cancer cell implantation and two times per week thereafter. Animals were pseudo-randomly assigned to one of three treatment groups: 1) M2M180N isotype (negative) control antibody, 2) M1M6977N anti-mouse GFR α 3 antibody, or 3) M1M6986N anti-mouse GFR α 3 antibody. M1M6986N blocks artemin's interaction with GFR α 3, and is thereby considered a "direct" blocker of artemin's action. In contrast, M1M6977N inhibits artemin's action through the GFR α 3/RET complex, and is therefore considered an "indirect" inhibitor.

Measures of Nociception

[0238] Nociceptive responses to the bone tumor were measured using the von Frey Hair test for evoked mechanical (tactile) allodynia, the dynamic weight bearing (DWB) test for willingness to bear weight on a limb, and guarding behavior. Von Frey test results are expressed as grams of pressure required for paw withdrawal. Weight bearing results are expressed as percent body weight placed on the ipsilateral limb. Guarding behavior is expressed as time spent guarding the limb over a two-minute period.

Results

Bone Destruction

[0239] There was no significant effect of antibody treatment on bone destruction score in this model, suggesting that the antibody treatment had no impact on the severity of the bone cancer itself.

Nociceptive Behavior

[0240] There was a statistically significant decrease in tactile allodynia with GFR α 3 antibody treatment after carcinoma ($F(2, 25)=8.626$, $p=.001$, Figure 5).

[0241] There were no statistically significant overall effects of GFR α 3 antibodies on dynamic weight bearing on the ipsilateral limb, although the overall effect of treatment achieved a statistical trend and M1M6977N achieved significant efficacy on post hoc comparison at 11 days (A), but not 18 days (B), after implantation of bone with carcinoma cells (11 day $F(2,25)=2.939$, $p=.071$, Figure 6A; 18 day $F(2,25)=0.149$, $p=.862$, Figure 6B).

[0242] GFR α 3 antibodies significantly reduced limb guarding after bone cancer implantation in

this model ($F(2,25)=4.222$, $p=.026$, Figure 7).

Conclusion

[0243] Treatment with anti-mouse GFR α 3 antibodies significantly reduced nociceptive behaviors in this bone cancer pain model as measured by evaluation of guarding and the von Frey Test of tactile allodynia. In addition, there was evidence of efficacy of the REGN1967 antibody in weight bearing differential at one time point. Bone destruction scores were not different in groups receiving anti-mouse GFR α 3 antibodies, suggesting that differences in pain-related measures could not be accounted for by differences in cancer severity. Therefore, our data suggest that neutralizing antibodies against GFR α 3 could be efficacious against bone cancer pain in this model of metastatic bone cancer pain.

Example 15. Destabilization of the Medial Meniscus (DMM) Model of Osteoarthritic Pain

Methodology

Subjects

[0244] Adult male mice on a C57Bl6 background strain were used for the DMM experiment starting at approximately 12 weeks of age. The experimenters measuring outcome data for this experiment were blind to treatment group of the animals throughout data collection, compilation, and analysis.

DMM Model

[0245] In the DMM model, the medial meniscus of one knee is destabilized and the animal is allowed to develop disease for 16 weeks. During the 16 week period, animals develop tactile allodynia and increases in bone volume and bone mineral content in the injured knee resembling early human osteoarthritis. Tactile allodynia was verified in animals by von Frey Test at 16 weeks before the initiation of antibody treatment.

Antibody Treatment

[0246] Each animal received 30mg/kg s.c. antibody injections administered weekly starting 16 weeks after DMM surgery. Animals were pseudo-randomly assigned to one of three treatment groups: 1) M2M180N isotype (negative) control antibody, 2) M1M6977N anti-mouse GFR α 3 antibody, or 3) M1M6986N anti-mouse GFR α 3 antibody. M1M6986N blocks artemin's interaction with GFR α 3, and is thereby considered a "direct" blocker of artemin's action. In

contrast, M1M6977N inhibits artemin's action through the GFR α 3/RET complex, and is therefore considered an "indirect" inhibitor.

Measures of Nociception

[0247] Nociceptive responses to the knee pathology were measured using the von Frey Hair test for evoked mechanical (tactile) allodynia.

Results

Nociceptive Behavior

[0248] There was a statistically significant decrease in tactile allodynia with GFR α 3 antibody treatment after DMM ($F(2, 27)=21.68$, $p=.0001$, Figure 8).

Conclusion

[0249] Treatment with mouse GFR α 3 antibodies had a statistically significant effect on tactile allodynia such that the groups treated with the two GFR α 3 antibodies consistently showed less allodynia than the isotype control starting 14 days after the initiation of weekly treatment. These data suggest the possibility that GFR α 3 antibodies will be efficacious against chronic human osteoarthritic pain.

Example 16. Cross-Competition Analysis of anti-GFR α 3 Antibodies

[0250] A cross-competition assay was conducted to assess the ability of select antibodies to compete with one another for binding to human GFR α 3 using an Octet RED384 biosensor (Fortebio Inc.). The entire experiment was performed at 25°C with the flow rate of 1000rpm in Octet HBST buffer (0.01 M HEPES pH7.4, 0.15M NaCl, 3 mM EDTA, 0.05% v/v Surfactant P20, 0.1mg/mL BSA). To assess whether 2 antibodies were able to compete with one another for binding to their respective epitopes on biotinylated recombinant human GFR α 3 expressed with a C-terminal myc-myc-hexahistidine tag (biotin-hGFR α 3-mmH; SEQ ID:370), around ~1.2nm of biotin-hGFR α 3-mmH was first captured onto streptavidin-coated Octet sensor tips (Fortebio Inc, # 18-5019) by submerging the tips for 1 minute into a 10 μ g/mL solution of biotin-hGFR α 3-mmH. The antigen coated sensor tips were then placed into wells containing 25 μ g/mL solution of a first anti-GFR α 3 monoclonal antibody for 4 minutes to saturate the biotin-hGFR α 3-mmH surface. The sensor tips were then subsequently dipped into wells containing 25 μ g/mL solution

of a second anti-GFR α 3 monoclonal antibody. The sensor tips were washed in Octet HBST buffer in between every step of the experiment. The real-time binding response was monitored during the course of the experiment and the binding response at the end of every step was recorded as shown in Figure 9. The response of mAb-2 binding to biotin-hGFR α 3-mmH pre-complexed with the first antibody was compared and competitive/non-competitive behavior of different anti-GFR α 3 monoclonal antibodies was determined.

[0251] As shown in Figure 9, dark grey boxes with black font represent binding response for self-competition. Antibodies competing in both directions, independent of the order of binding are represented with black boxes and white font. No competition between antibodies that suggest distinct binding epitope is represented as white box with black font.

[0252] Nine antibodies (H4H2236N3, H4H2342P, H4H2295S, H4H2294S, H4H2291S, H4H2357S, H4H2355S, H4H2296S, and H4H2243N2) bi-directionally compete with each other for binding to biotin-hGFR α 3-mmH. Eight of the 9 (H4H2236N3, H4H2342P, H4H2295S, H4H2294S, H4H2291S, H4H2357S, H4H2355S, and H4H2296S) do not compete with any other anti-GFR α 3 antibody tested, while H4H2243N2 also bi-directionally competes with two additional anti-GFR α 3 antibodies tested (H4H2212N and H4H2352S). H4H2212N and H4H2352S bi-directionally compete with each other and H4H2243N2 for binding to biotin-hGFR α 3-mmH, but while H4H2212N does not compete with any other anti-GFR α 3 antibodies tested, H4H2352S also bi-directionally competes with an additional anti-GFR α 3 antibody tested (H4H2292S). One anti-GFR α 3 antibody tested, H4H2350P, does not compete with any of the anti-GFR α 3 antibodies tested for binding to biotin-hGFR α 3-mmH.

8300A-WO SEQUENCE LISTING

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<120> Human Antibodies to GFR-alpha-3 and Methods of Use Thereof

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Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
1 5

<210> 49

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 49

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caggttcaac tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcttgcaagg cttctgggta caccctttacc agctatggta tcatctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa cacaaactat 180
gcacagaatc tccagggcag agtcaccatg accacagaca cttccacgac cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagatggggg 300
atagcaactc gtccctacta ctactacggt atggacgtct ggggcccaagg gaccacggtc 360
accgtctcct ca 372
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<210> 50

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 50

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Gly	Ile	Ile	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Trp	Ile	Ser	Gly	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Asn	Leu
	50					55					60				
Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Thr	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85				90						95	
Ala	Arg	Trp	Gly	Ile	Ala	Thr	Arg	Pro	Tyr	Tyr	Tyr	Tyr	Gly	Met	Asp
			100					105					110		
Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser				
		115					120								

<210> 51

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 51

ggttacacct ttaccagcta tgggt 24

<210> 52

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 52

Gly	Tyr	Thr	Phe	Thr	Ser	Tyr	Gly
1				5			

<210> 53

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 53

atcagcgggtt acaatggtaa caca 24

<210> 54

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 54

Ile	Ser	Gly	Tyr	Asn	Gly	Asn	Thr
1				5			

<210> 55

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 55

gcgagatggg	gtatagcaac	tcgtccctac	tactactacg	gtatggacgt	c	51
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<210> 56

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 56

Ala	Arg	Trp	Gly	Ile	Ala	Thr	Arg	Pro	Tyr	Tyr	Tyr	Tyr	Gly	Met	Asp
1				5				10					15		
Val															

<210> 57

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 57

gacatccaga	tgacccagtc	tocatcctca	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcaattgtc	gggagagtc	ggacattacc	aattatttag	cctggtttca	gcagaaacca	120
gggaaagccc	ctaagtcctt	gatctatget	gcattccagt	tgcaaagtgg	ggtcccatca	180
aagttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ctgccaacag	tataatagtt	accctccac	tttcggccct	300
gggaccaaaag	tgatatcaaa	a				321

<210> 58
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 58
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Thr Asn Tyr
 20 25 30
 Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
 85 90 95
 Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 59
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 59
 caggacatta ccaattat 18

<210> 60
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 60
 Gln Asp Ile Thr Asn Tyr
 1 5

<210> 61
 <211> 9
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Synthetic

<400> 61

gctgcatcc 9

<210> 62

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 62

Ala Ala Ser
1

<210> 63

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 63

caacagtata atagttaccc tccact 27

<210> 64

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 64

Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
1 5

<210> 65

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 65

gagggtgcagc tgttggagtc tgggggaggc ttggtacagc cggggggggtc cctgagagtc 60
tctgtgtcag cctctggatt caccttttagc acctctgcc a tgagctgggt cgcagcaggt 120

```

ccaggggaagg ggcttgagtg ggtctcaggt attagtggta ttggaggtgg tagcacatac 180
tacgcagact cegtgaaggg cgggttcacc atctccagag acaattccaa gaacacgctg 240
tatctgcaaa tgaacagcct gagagccgag gacacggccg tatatttctg tgcgaaattt 300
tataagtgga attcatatat ttttgatctc tggggccagg ggacaatggg caccgtctct 360
tca                                     363

```

<210> 66

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 66

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1          5          10          15
Ser Leu Arg Val Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Ser
20          25          30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35          40          45
Ser Gly Ile Ser Gly Ile Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
50          55          60
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65          70          75          80
Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe
85          90          95
Cys Ala Lys Phe Tyr Lys Trp Asn Ser Tyr Ile Phe Asp Leu Trp Gly
100         105         110
Gln Gly Thr Met Val Thr Val Ser Ser
115          120

```

<210> 67

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 67

```

ggattcacct ttagcacctc tgcc          24

```

<210> 68

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 68

```

Gly Phe Thr Phe Ser Thr Ser Ala
1          5

```

<210> 69

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 69

attagtggta ttgaggtgg tagcaca 27

<210> 70

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 70

Ile Ser Gly Ile Gly Gly Gly Ser Thr
1 5

<210> 71

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 71

gcgaaatttt ataagtgga ttcatatatt ttgatctc 39

<210> 72

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 72

Ala Lys Phe Tyr Lys Trp Asn Ser Tyr Ile Phe Asp Leu
1 5 10

<210> 73

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 73

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gaaattgtgt tgacgcagtc tccagacacc ctatctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtc gagtgtagt agcagctact ttgcctggta ccagcagaag 120
cctggccagg ctcccaggct cctcatgtat agtgcacca gcagggccac tggcatccca 180
gacaggttca gtggcagtg gtctgggaca gacttctctc tcaccatcag cagattggag 240
cctgaagatt ttgcagtgt ttactgtcag cagtatggta ggtcactcac tttcggcgga 300
gggaccaagg tggagatcaa g                                     321

```

<210> 74

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 74

```

Glu Ile Val Leu Thr Gln Ser Pro Asp Thr Leu Ser Leu Ser Pro Gly
 1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
          20           25           30
Tyr Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35           40           45
Met Tyr Ser Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
       50           55           60
Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Ser Arg Leu Glu
 65           70           75           80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Arg Ser Leu
          85           90           95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        100           105

```

<210> 75

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 75

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cagagtgtta gtagcagcta c          21

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<210> 76

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 76

Gln Ser Val Ser Ser Ser Tyr
 1 5

<210> 77

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 77

agtgcattcc 9

<210> 78

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 78

Ser Ala Ser
 1

<210> 79

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 79

cagcagtatg gtaggtcact cact 24

<210> 80

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 80

Gln Gln Tyr Gly Arg Ser Leu Thr
 1 5

<210> 81

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 81

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gaggtgcagc tgttgaggc tgggggaggc ttggtacagt ctgggggggc actgagactc 60
tcctgtgcag cctctggatt cagctttaac aactatgcca tgagctgggt ccgccagget 120
ccagggaagg ggctggagtg ggtctcattt attagtggta gtggtggtag tacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa tacgctgtat 240
ctgcaaataa acagcctgag agtcgaggac acggccggtt ttactgtgc gaaagacaga 300
tacaactatg gtaccttctt tgactactgg ggccaggga ccttggtcac cgtctctca 360

```

<210> 82

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 82

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Ser Gly Gly
 1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Asn Asn Tyr
 20           25           30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35           40           45
Ser Phe Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65           70           75           80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val Phe Tyr Cys
 85           90           95
Ala Lys Asp Arg Tyr Asn Tyr Gly Thr Phe Phe Asp Tyr Trp Gly Gln
100          105          110
Gly Thr Leu Val Thr Val Ser Ser
115          120

```

<210> 83

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 83

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ggattcagct ttaacaacta tgcc      24

```

<210> 84

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 84

Gly Phe Ser Phe Asn Asn Tyr Ala
1 5

<210> 85

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 85

attagtggta gtggtgtag taca 24

<210> 86

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 86

Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 87

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 87

gcgaaagaca gatacaacta tggtagcttc ttgactac 39

<210> 88

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 88

Ala Lys Asp Arg Tyr Asn Tyr Gly Thr Phe Phe Asp Tyr
 1 5 10

<210> 89

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 89

gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
 atcaactgca aatccagcca gagtggttta tacagctcca acaataagaa ctacttaact 120
 tggtaaccagc agaaaccagg acagcctcct aaattgctca tttactgggc atctaccggg 180
 gaatccggggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
 atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtact 300
 cctccgacgt tggcctagg gaccaagggtg gaaatcaaa 339

<210> 90

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 90

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
 20 25 30
 Ser Asn Asn Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60
 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
 85 90 95
 Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Leu Gly Thr Lys Val Glu Ile
 100 105 110
 Lys

<210> 91

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 91

cagagtgttt tatacagctc caacaataag aactac 36

<210> 92
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 92
 Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
 1 5 10

<210> 93
 <211> 9
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 93
 tgggcatct 9

<210> 94
 <211> 3
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 94
 Trp Ala Ser
 1

<210> 95
 <211> 27
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 95
 cagcaatatt atagtactcc tccgacg 27

<210> 96
 <211> 9
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 96

Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
1 5

<210> 97

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 97

gaagtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggagtc cctgagactc 60
tcctgtgcag cctctggatt cacccttagc aactatgcc a tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagtt attagtggta gtggtggtag cacatactac 180
gcagactccg tgaagggccg gttcaccatg tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaacccccg 300
agtagagcag ctcgatactt caactacggt atggacgtct ggggcccaagg gaccacggtc 360
accgtctcct ca 372

<210> 98

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 98

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Glu
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Val Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Pro Pro Ser Arg Ala Ala Arg Tyr Phe Asn Tyr Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 99

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 99

ggattcacct ttagcaacta tgcc 24

<210> 100

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 100

Gly Phe Thr Phe Ser Asn Tyr Ala
1 5

<210> 101

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 101

attagtggta gtggtggtag caca 24

<210> 102

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 102

Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 103

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 103

gcgaaacccc cgagtagagc agctcgatac ttcaactacg gtatggacgt c 51

<210> 104

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 104

Ala	Lys	Pro	Pro	Ser	Arg	Ala	Ala	Arg	Tyr	Phe	Asn	Tyr	Gly	Met	Asp
1				5				10						15	
Val															

<210> 105

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 105

gccatccgga	tgacccagtc	cccatcttcc	gtgtctgcat	ctgtaggaga	cagagtcacc	60
atcaattgtc	gggcgagtc	gggtattagc	agctggttag	cctggatatca	gcagaaacca	120
gggaaagccc	ctaagctcct	gatctatgct	gcattccagtt	tgcaaagtgg	ggteccatca	180
aggttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
gaagattttg	caacttacta	ttgtcaacag	gctaacagtt	tcccgttcac	tttcggcgga	300
gggaccaagg	tgagatcaa	a				321

<210> 106

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 106

Ala	Ile	Arg	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5				10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp
		20					25				30				
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35				40				45					
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50				55			60							
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70				75					80		
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ala	Asn	Ser	Phe	Pro	Phe
			85				90						95		
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
		100					105								

<210> 107

<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 107
caggggtatta gcagctgg 18

<210> 108
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 108
Gln Gly Ile Ser Ser Trp
1 5

<210> 109
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 109
gctgcatcc 9

<210> 110
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 110
Ala Ala Ser
1

<210> 111
<211> 27
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 111

caacaggcta acagttccc gttcact 27

<210> 112

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 112

Gln	Gln	Ala	Asn	Ser	Phe	Pro	Phe	Thr
1			5					

<210> 113

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 113

gaagtgcagc	tgggtggagtc	tggggggaggc	gtgggtccagc	ctgggagggtc	cctgagactc	60
tactgtgcag	cgtctggatt	caccttcagt	agctatggca	tgcactgggt	cggccaggct	120
cggggcaagg	ggctggagtg	ggtgtcattt	atatgggatg	atggaagtaa	taaatactat	180
gcagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaataa	acagcctgac	agccgaggac	acggctgtat	attattgtgc	gagaagaggt	300
atcctaactg	gaactaccgc	ttttgatatc	tggggccaag	ggacaatggg	caccgtctct	360
tca						363

<210> 114

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 114

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
1			5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
		20						25					30		
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35				40						45			
Ser	Phe	Ile	Trp	Tyr	Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
	50				55					60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65				70				75						80	
Leu	Gln	Met	Asn	Ser	Leu	Thr	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys

				85					90					95	
Ala	Arg	Arg	Gly	Ile	Leu	Thr	Gly	Thr	Thr	Ala	Phe	Asp	Ile	Trp	Gly
			100					105					110		
Gln	Gly	Thr	Met	Val	Thr	Val	Ser	Ser							
		115					120								

<210> 115

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 115

ggattcacct tcagtagcta tggc 24

<210> 116

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 116

Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Gly
1				5			

<210> 117

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 117

atatggtatg atggaagtaa taaa 24

<210> 118

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 118

Ile	Trp	Tyr	Asp	Gly	Ser	Asn	Lys
1				5			

<210> 119

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 119

gcgagaagag gtatcctaac tggaactacc gcttttgata tc 42

<210> 120

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 120

Ala	Arg	Arg	Gly	Ile	Leu	Thr	Gly	Thr	Thr	Ala	Phe	Asp	Ile
1				5				10					

<210> 121

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 121

gacatccaga	tgacccagtc	tcatacctcc	ctgtctgcat	ctgtgggaga	cagagtcacc	60
atcacttgcc	gggcaagtca	gagcattagc	agttatttga	attggatatca	gcagaaacca	120
gggaaagccc	ctaagctcct	gatctatgct	gcataccagtt	tgcaaagtgg	ggccccatca	180
aggttcagtg	gcagtggtac	tgggacagat	ttoactctca	ccatccggag	tctgatacct	240
gaagattttg	caacttacta	ctgtcaacag	acttacaata	ccccattcac	tttcggccct	300
gggaccaag	tggaatcaa	a				321

<210> 122

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 122

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr
			20					25				30			
Leu	Asn	Trp	Trp	Gln	Gln	Lvs	Pro	Glv	Lvs	Ala	Pro	Lvs	Leu	Leu	Ile

```

-----
      35      40      45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
      50      55      60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Arg Ser Leu Ile Pro
65      70      75      80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Asn Thr Pro Phe
      85      90      95
Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
      100      105

```

<210> 123

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 123

cagagcatta gcagttat 18

<210> 124

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 124

```

Gln Ser Ile Ser Ser Tyr
1           5

```

<210> 125

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 125

gctgcatcc 9

<210> 126

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 126

Ala Ala Ser

1

<210> 127

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 127

caacagactt acaatacccc attcact 27

<210> 128

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 128

Gln Gln Thr Tyr Asn Thr Pro Phe Thr

1

5

<210> 129

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 129

```

cagggtgcagc tgggtggagtc tggggggaggc gtgggtccagc ctgggagggtc cctgagactc 60
tccgtgtgcag cgtctggatt cagtttcagt gactatgtca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcatct atatggtttg atggaagtaa tgaactctat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc gaaaaaggga 300
gttttggtag ctacctctgc ttttcataac tggggccaag ggacaatggc caccgtctct 360
tca
363

```

<210> 130

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 130

```

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr
      20           25           30
Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35           40           45
Ala Ser Ile Trp Phe Asp Gly Ser Asn Glu Leu Tyr Ala Asp Ser Val
      50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
      65           70           75           80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85           90           95
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe His Ile Trp Gly
      100          105          110
Gln Gly Thr Met Val Thr Val Ser Ser
      115          120

```

<210> 131

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 131

ggattcagtt tcagtgacta tgtc 24

<210> 132

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 132

```

Gly Phe Ser Phe Ser Asp Tyr Val
 1           5

```

<210> 133

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 133

atatggtttg atggaagtaa tgaa 24

<210> 134

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 134

Ile	Trp	Phe	Asp	Gly	Ser	Asn	Glu
1				5			

<210> 135

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 135

gcgaaaaagg	gagtttggg	agctacctct	gctttcata	tc	42
------------	-----------	------------	-----------	----	----

<210> 136

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 136

Ala	Lys	Lys	Gly	Val	Leu	Val	Ala	Thr	Ser	Ala	Phe	His	Ile
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

1		5		10
---	--	---	--	----

<210> 137

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 137

gccatccaga	tgacccagtc	tcatactctc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcacttgcc	gggcaagtc	gaacattaac	aactatttaa	attggtatca	tcagaaacca	120
gggaaagccc	ctaattctct	aatttatgct	gcattccagt	tgcaaagtgg	ggccccatca	180
aggttcagtg	gcagtgatc	tgggacagat	tacactctca	ccatcagcag	tctgcaacct	240
gaagattttg	gaaattacta	ctgtcaacag	agttacagca	cttccatgta	cacttttggc	300
caggggacca	agctggagat	caaa				324

<210> 138

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 138

```

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Asn Asn Tyr
      20             25             30
Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
      35             40             45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
      50             55             60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65             70             75             80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Ser Met
      85             90             95
Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100             105

```

<210> 139

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 139

cagaacatta acaactat 18

<210> 140

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 140

```

Gln Asn Ile Asn Asn Tyr
 1             5

```

<210> 141

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 141

gctgcatcc 9

<210> 142

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 142

Ala Ala Ser
1

<210> 143

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 143

caacagagtt acagcacttc catgtacact 30

<210> 144

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 144

Gln Gln Ser Tyr Ser Thr Ser Met Tyr Thr
1 5 10

<210> 145

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 145

```

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tctgtgcag cctctggatt caccitttagc agctatgccg tgagctgggt ccgccagget 120
ccagggaagg ggctggagtg ggtctcagtt attagtggta gtggaggtag cacatactac 180
gcagacgccg tgaagggccg gttcaccatc tccagagaca attccaagca cacgctgtat 240

```

```

ctgcaaataa acagcctgag agccgaggac acggccgtat attactgtac gaaaccctca 300
tattatagca gttcgaactt ctattatggg atggacgtct ggggccaagg gtccacggtc 360
accgtctcct ca                                     372

```

<210> 146

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 146

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
      20             25             30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35             40             45
Ser Val Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ala Val
      50             55             60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys His Thr Leu Tyr
      65             70             75             80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85             90             95
Thr Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
      100            105            110
Val Trp Gly Gln Gly Ser Thr Val Thr Val Ser Ser
      115            120

```

<210> 147

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 147

```

ggattcacct ttagcagcta tgcc          24

```

<210> 148

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 148

```

Gly Phe Thr Phe Ser Ser Tyr Ala
 1             5

```

<210> 149

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 149

attagtggta gtggaggtag caca 24

<210> 150

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 150

Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 151

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 151

acgaaacct catctatag cagttcgaac ttctattatg gtatggacgt c 51

<210> 152

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 152

Thr Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
1 5 10 15
Val

<210> 153

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 153

```

gacatccagt tgacccagtc tocatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtc gggattagc agctggtag cctggatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatget gcattccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcagcag actaacagtt tccattccc ttctggccct 300
gggaccaaag tggatatcaa a 321

```

<210> 154

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 154

```

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20          25          30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35          40          45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50          55          60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Asn Ser Phe Pro Phe
85          90          95
Pro Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100         105

```

<210> 155

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 155

```

cagggattta gcagctgg 18

```

<210> 156

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 156

```

Gln Gly Ile Ser Ser Trp

```

1

5

<210> 157

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 157

gctgcatcc 9

<210> 158

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 158

Ala Ala Ser
1

<210> 159

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 159

cagcagacta acagtttccc attccct 27

<210> 160

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 160

Gln Gln Thr Asn Ser Phe Pro Phe Pro
1 5

<210> 161

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 161

```

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagg ctgggggggtc cctgagactc 60
tcctgtgtag cctctggatt caccttttagc agctatgcca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactcc 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaataa acagcctgag agccgaggac acggccgtat attactgtac gaaaccctca 300
tcttatagca gctcgaactt ctactacggt atggacgtct ggggcccaagg gaccacggtc 360
accgtctcct ca                                     372

```

<210> 162

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 162

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1           5           10           15
Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20           25           30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35           40           45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Ser Ala Asp Ser Val
50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65           70           75           80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85           90           95
Thr Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
100          105          110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115          120

```

<210> 163

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 163

```

ggattcacct ttagcagcta tgcc          24

```

<210> 164

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 164

Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 165

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 165

attagtggta gtggtgtag caca 24

<210> 166

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 166

Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 167

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 167

acgaaaccct catcttatag cagctcgaac ttctactacg gtatggacgt c 51

<210> 168

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 168

Thr Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
 1 5 10 15
 Val

<210> 169

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 169

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgtc gggcgagtc ggggtattag agctgggttag cctgggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctatact gcattccagtt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc taggacagat ttcaactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttacta ttgtcaacag actaacagtc tcccactcac ttteggccct 300
 gggaccaagg tggagatcaa a 321

<210> 170

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 170

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Thr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Asn Ser Leu Pro Leu
 85 90 95
 Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 171

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 171

cagggtatta gcagctgg 18

<210> 172

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 172

Gln	Gly	Ile	Ser	Ser	Trp
1				5	

<210> 173

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 173

actgcatcc	9
-----------	---

<210> 174

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 174

Thr	Ala	Ser
1		

<210> 175

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 175

caacagacta	acagtctccc	actcact	27
------------	------------	---------	----

<210> 176

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 176

Gln Gln Thr Asn Ser Leu Pro Leu Thr
 1 5

<210> 177

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 177

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
 tectgtgcag cctctggatt caccttttagc agctatgcca tgagctgggt cggccaggct 120
 ccagggaagg ggctggagtg ggtctcagtt attagtggta gtgggtggtag cacatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctacaaatga acagcctgag agccgaggac acggccgttt attactgtgc gaaaccctca 300
 tcttatagca gctcgaactt ctactacggt atggacgtct gggggccaagg gaccacggtc 360
 accgtctcct ca 372

<210> 178

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 178

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Val Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe Tyr Tyr Gly Met Asp
 100 105 110
 Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 179

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 179

ggattcacct ttagcagcta tgcc 24

<210> 180

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 180

Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 181

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 181

attagtggta gtggtggtag caca 24

<210> 182

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 182

Ile Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 183

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 183

gcgaaaccct catcttatag cagctcgaac ttctactacg gtatggacgt c 51

<210> 184

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 184

Ala	Lys	Pro	Ser	Ser	Tyr	Ser	Ser	Ser	Asn	Phe	Tyr	Tyr	Gly	Met	Asp
1				5				10					15		
Val															

<210> 185

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 185

gacatcgtga	tgacccagtc	tcacatcttcc	gtgtctgcat	ctgtaggaga	cagagtcacc	60
atcacttgtc	gggcgagtc	gggtattagc	agctggttag	cctgggtatca	gcagaaacca	120
gggaaagccc	ctaagctcct	gatctatgct	gcacccagtt	tgogaagtgg	gggtcccatca	180
aggttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcaccag	cctgcagcct	240
gaagattttg	caacttacta	ttgtcaacac	actaacagtt	tcccattcac	tttcggccct	300
gggaccaag	tgagatcaa	a				321

<210> 186

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 186

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5				10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp
		20						25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Ala	Ala	Ser	Ser	Leu	Arg	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
		50				55				60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Thr	Ser	Leu	Gln	Pro
65					70					75				80	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Thr	Asn	Ser	Phe	Pro	Phe
				85				90						95	
Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

<210> 187

<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 187
caggggtatta gcagctgg 18

<210> 188
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 188
Gln Gly Ile Ser Ser Trp
1 5

<210> 189
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 189
gctgcatcc 9

<210> 190
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 190
Ala Ala Ser
1

<210> 191
<211> 27
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 191

caacacacta acagttccc attcact 27

<210> 192

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 192

Gln	His	Thr	Asn	Ser	Phe	Pro	Phe	Thr
1				5				

<210> 193

<211> 369

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 193

gagggtgcagc	tgggtggagtc	tggggctgag	gtgaagaagt	ctgggtcctc	ggtgaaggtc	60
tectgcaagg	cttctggagg	caccttcagc	cgctatgcta	tcagctgggt	gcgacaggcc	120
cctggacaag	ggcttgagtg	gatgggaggg	atcatccctc	tcttttgtac	attaaactac	180
gcacagaagt	tccagggcag	agtcacgctt	accacggacg	aatcaacgag	cacagcctac	240
atggagctga	gcagcctgag	atctgaggac	acggccgtgt	attactgtgc	ggtattttac	300
tatggttcgg	ggagttatcg	caactgggtc	gacccctggg	gccagggaac	cctggtcacc	360
gtctctctca						369

<210> 194

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 194

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Ala	Glu	Val	Lys	Lys	Ser	Gly	Ser
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Ser	Arg	Tyr
			20					25					30		
Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35				40					45			
Gly	Gly	Ile	Ile	Pro	Leu	Phe	Gly	Thr	Leu	Asn	Tyr	Ala	Gln	Lys	Phe
			50			55				60					
Gln	Gly	Arg	Val	Thr	Leu	Thr	Thr	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr
					70					75				80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys

				85				90					95		
Ala	Val	Phe	Tyr	Tyr	Gly	Ser	Gly	Ser	Tyr	Arg	Asn	Trp	Phe	Asp	Pro
			100					105					110		
Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser					
		115					120								

<210> 195

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 195

ggaggcacct tcagccgcta tgct 24

<210> 196

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 196

Gly	Gly	Thr	Phe	Ser	Arg	Tyr	Ala
1				5			

<210> 197

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 197

atcatccctc tctttgtac atta 24

<210> 198

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 198

Ile	Ile	Pro	Leu	Phe	Gly	Thr	Leu
1				5			

<210> 199

<211> 48

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 199

gcggtatattt actatgggtc ggggagttat cgcaactggt tcgacccc 48

<210> 200

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 200

Ala	Val	Phe	Tyr	Tyr	Gly	Ser	Gly	Ser	Tyr	Arg	Asn	Trp	Phe	Asp	Pro
1				5				10					15		

<210> 201

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 201

gacatccaga	tgacccagtc	tcacatctcc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcacttgcc	gggcaagtca	gagcatcagc	agctatttaa	attgggtatca	gcagaaacca	120
gggaaagccc	ctaagctcct	gatctatgct	gcattccagt	tgcaaagtgg	ggtcccatca	180
aggttcagtg	gcagtggatc	tgggacagat	ttaactctca	ccatcagcag	tctgcaacct	240
gaagattttg	caacttacca	ctgtcaacag	agttacagta	tcccgatcac	cttcggccaa	300
gggacacgac	tggagattaa	a				321

<210> 202

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 202

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr
			20				25					30			
Leu	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile

```

Asp 100  Asp 110  Ser 120  Ser 130  His 140  Leu 150  Gly 160  Lys 170  Ala 180  Lys 190  Asp 200  Asp 210  Leu
    35              40              45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50              55              60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65              70              75              80
Glu Asp Phe Ala Thr Tyr His Cys Gln Gln Ser Tyr Ser Ile Pro Ile
    85              90              95
Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
    100              105

```

<210> 203

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 203

cagagcatca gcagctat 18

<210> 204

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 204

```

Gln Ser Ile Ser Ser Tyr
 1              5

```

<210> 205

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 205

gctgcatcc 9

<210> 206

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 206

Ala Ala Ser
1

<210> 207

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 207

caacagagtt acagtatccc gatcacc 27

<210> 208

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 208

Gln Gln Ser Tyr Ser Ile Pro Ile Thr
1 5

<210> 209

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 209

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gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacccttagc acctatgcc a tgagctgggt ccgccaggt 120
ccagggaagg ggcctggaatg ggtctcagct attcgtggta atgggtgttaa cacatactac 180
ggagactcca tgaagggccg tttcaccatc tccagagaca attccaagga caccgtgtat 240
ttgcaaataa acagcctgag agccgaggac acggccgtat attactgtgc gaaaaataaa 300
tgggagctgc tagtctttga atactggggc cagggaaccc tggtcaccgt ctctca 357

```

<210> 210

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 210

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1			5					10					15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Thr	Tyr
		20					25					30			
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35					40						45			
Ser	Ala	Ile	Arg	Gly	Asn	Gly	Val	Asn	Thr	Tyr	Tyr	Gly	Asp	Ser	Met
	50				55						60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asp	Thr	Leu	Tyr
65					70					75				80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90					95		
Ala	Lys	Asn	Lys	Trp	Glu	Leu	Leu	Val	Phe	Glu	Tyr	Trp	Gly	Gln	Gly
		100						105					110		
Thr	Leu	Val	Thr	Val	Ser	Ser									
	115														

<210> 211

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 211

ggattcacct ttagcaccta tgcc 24

<210> 212

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 212

Gly Phe Thr Phe Ser Thr Tyr Ala

1

5

<210> 213

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 213

attcgtggta atggtgtaa caca 24

<210> 214

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 214

Ile	Arg	Gly	Asn	Gly	Val	Asn	Thr
1				5			

<210> 215

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 215

gcgaaaaata aatgggagct gctagtcttt gaatac 36

<210> 216

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 216

Ala	Lys	Asn	Lys	Trp	Glu	Leu	Leu	Val	Phe	Glu	Tyr
1				5					10		

<210> 217

<211> 318

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 217

```

gacatccaga tgacccagtc tocatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcgagtcg ggacattagc aattatttag cctggatca gcagaaacca 120
gggaaagttc ctaagctcct gatctatgct gcattccact tgcaatcagg ggteccattt 180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagatgttg caacttatta ctgtcaaaag tataacagtg cccctccttt cggccctggg 300
accaaagtgg atatcaaa                                     318

```

<210> 218

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 218

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1          5          10          15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
          20          25          30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
          35          40          45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Phe Arg Phe Ser Gly
          50          55          60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80
Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Pro
          85          90          95
Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
          100          105

```

<210> 219

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 219

caggacatta gcaattat 18

<210> 220

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 220

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Gln Asp Ile Ser Asn Tyr
 1          5

```

<210> 221

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 221

gctgcatcc 9

<210> 222

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 222

Ala Ala Ser
1

<210> 223

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 223

caaaagtata acagtgtccc tcct 24

<210> 224

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 224

Gln Lys Tyr Asn Ser Ala Pro Pro
1 5

<210> 225

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 225

gaggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tctgtgtcag cgtctggatt cagtttcagt gactatgtca tgcactgggt ccgccaggct 120
ccaggcaagg ggcctggagtg ggtggcatct atatggtttg atggaagtaa tgaattctat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaataa acagtctgag agccgaggac acggctgtgt attactgtgc gaaaaaggga 300
gtgttggtag ctacctctgc ttttgatata tggggccaag ggacaatggt caccgtctct 360

tca

363

<210> 226

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 226

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr
      20             25             30
Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35             40             45
Ala Ser Ile Trp Phe Asp Gly Ser Asn Glu Phe Tyr Ala Asp Ser Val
      50             55             60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
      65             70             75             80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85             90             95
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile Trp Gly
      100            105            110
Gln Gly Thr Met Val Thr Val Ser Ser
      115            120

```

<210> 227

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 227

ggattcagtt tcagtgacta tgtc 24

<210> 228

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 228

```

Gly Phe Ser Phe Ser Asp Tyr Val
 1             5

```

<210> 229

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 229

atatggttg atggaagtaa tgaa 24

<210> 230

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 230

Ile Trp Phe Asp Gly Ser Asn Glu
1 5

<210> 231

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 231

gcgaaaaagg gagtgttggt agctacctct gctttgata tc 42

<210> 232

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 232

Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile
1 5 10

<210> 233

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 233

gacatccaga tgaccacgac tccatctccc ctgtctgcat ctgtaggaga cagagtcacc 60

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atcacttgcc gggcaagtca gagcattaac aactatttaa attggtatca tcagaaacca 120
gggaaagccc ctaagctcct aatctatget gcattccagtt tgcaaagtgg ggtcccatca 180
agggttcagt gcagtggatc tgggacagat tacactctca ccatcagcag tctgcaacct 240
gaagattttg gaaattacta ctgtcaacag agttacagaa cttccatgta cacttttggc 300
caggggacca aggtggaaat caaaa                                324

```

<210> 234

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 234

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Tyr
20        25        30
Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35        40        45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50        55        60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65        70        75        80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Ser Met
85        90        95
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100       105

```

<210> 235

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 235

cagagcatta acaactat 18

<210> 236

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 236

```

Gln Ser Ile Asn Asn Tyr
1           5

```

<210> 237
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 237
gctgcatcc 9

<210> 238
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 238
Ala Ala Ser
1

<210> 239
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 239
caacagagtt acagaacttc catgtacact 30

<210> 240
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 240
Gln Gln Ser Tyr Arg Thr Ser Met Tyr Thr
1 5 10

<210> 241
<211> 360
<212> DNA

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> Synthetic

<400> 241

gaggtgcagc	tggtggagtc	tgggggaggc	ttggtacggc	ctggcaggtc	cctgagaactc	60
tcctgtgcag	cctctggatt	cacctttgat	aattatgcc	tgcactgggt	cgggcaagtt	120
ccagggaagg	gcctggagtg	ggtctcaggt	attacttga	atagtgttag	cctaggctat	180
gcggaactctg	tgaagggcg	attcaccatc	tccagagaca	acgccagaa	ctcctgtat	240

ctgcaaatga acagttctgag aactgtggac acggccttgt attactgtgc aaaagatagg 300
tggggtggaa gttactactt tgactttctgg ggccaggga ccttggtcac cgtctcctca 360

 $\langle 210 \rangle$ 242

$\langle 211 \rangle$ 120

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Synthetic

<400> 242

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Arg	Pro	Gly	Arg
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asp	Asn	Tyr
			20					25					30		
Ala	Met	His	Trp	Val	Arg	Gln	Val	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35				40						45			
Ser	Gly	Ile	Thr	Trp	Asn	Ser	Val	Ser	Leu	Gly	Tyr	Ala	Asp	Ser	Val
	50				55						60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Gln	Asn	Ser	Leu	Tyr
65					70				75					80	
Leu	Gln	Met	Asn	Ser	Leu	Arg	Thr	Val	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys
			85						90					95	
Ala	Lys	Asp	Arg	Trp	Gly	Gly	Ser	Tyr	Tyr	Phe	Asp	Phe	Trp	Gly	Gln
			100					105					110		
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser								
		115				120									

 $\langle 210 \rangle$ 243

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 243

ggattcacct ttgataatta tgcc 24

<210> 244

 $\langle 211 \rangle$ 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 244

Gly	Phe	Thr	Phe	Asp	Asn	Tyr	Ala
1				5			

<210> 245

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 245

attacttgga	atagtgtag	ccta	24
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<210> 246

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 246

Ile	Thr	Trp	Asn	Ser	Val	Ser	Leu
1			5				

<210> 247

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 247

gcaaaagata	ggtggggtgg	aagttactac	tttgacttc	39
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<210> 248

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 248

Ala Lys Asp Arg Trp Gly Gly Ser Tyr Tyr Phe Asp Phe
 1 5 10

<210> 249

<211> 318

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 249

gacatcgtga tgacccagtc tocatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgcc gggcgagtca gggcattagc aattatttag cctgggtatca gcagaaacca 120
 gggaaagtgc ctaaactcct gatctattct gcattccactt tgcaatcagg ggtcccatct 180
 cggttcagtg gcagtggatc tgggacagat ttcaactctca ccatcagcaa cctgcagcct 240

gaagattttg caactttttt ctgtcaaaag tataacagtg cccccacttt cggcggaggg 300
 accaaggtgg agatcaaa 318

<210> 250

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 250

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Val Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ser Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Phe Phe Cys Gln Lys Tyr Asn Ser Ala Pro Thr
 85 90 95
 Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 251

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 251

cagggcatta gcaattat 18

<210> 252

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 252

Gln Gly Ile Ser Asn Tyr
1 5

<210> 253

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 253

tctgcatcc 9

<210> 254

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 254

Ser Ala Ser
1

<210> 255

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 255

caaaagtata acagtgtccc cact 24

<210> 256

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 256

Gln Lys Tyr Asn Ser Ala Pro Thr
 1 5

<210> 257

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 257

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cagggtgcagc tgggtggagtc tggggggaggc gtgggtccagc ctgggagggtc cctgagactc 60
tccgtgtgcag cgtctggatt cagtttcagt gactatgtca tgcactgggt ccgccaggct 120
ccaggcaagg ggcctggagtg ggtggcatct atatggtttg atggaagtaa tgaattctat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgttt 240
ctgcaaatga acagtctgag agccgaggac acggctgtgt attactgtgc gaaaaaggga 300
gtgttggttag ctacctctgc ttttgatata tggggccaag ggacaatggt caccgtctct 360
tca 363

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<210> 258

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 258

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr
 20      25      30
Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35      40      45
Ala Ser Ile Trp Phe Asp Gly Ser Asn Glu Phe Tyr Ala Asp Ser Val
 50      55      60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
 65      70      75      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85      90      95
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile Trp Gly
 100     105     110
Gln Gly Thr Met Val Thr Val Ser Ser
 115     120

```

<210> 259

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 259

ggattcagtt tcagtgacta tgtc 24

<210> 260

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 260

Gly Phe Ser Phe Ser Asp Tyr Val
1 5

<210> 261

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 261

atatggttg atggaagtaa tgaa 24

<210> 262

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 262

Ile Trp Phe Asp Gly Ser Asn Glu
1 5

<210> 263

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 263

gcgaaaaagg gagtgttggt agctacctct gctttgata tc 42

<210> 264

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 264

Ala	Lys	Lys	Gly	Val	Leu	Val	Ala	Thr	Ser	Ala	Phe	Asp	Ile
1				5									10

<210> 265

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 265

gaaattgtga	tgaacgcagtc	tccatcctcc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcacttgcc	gggcaagtca	gagcattaac	aactatttaa	attggtatca	tcagaaacca	120
gggaaagccc	ctaagctcct	aatctatgct	gcaccagtt	tgcaaagtgg	ggtoccatca	180
aggttcagtg	gcagtggatc	tgggacagat	tacactctca	ccatcagcag	totgcaacct	240
gaagattttg	gaaattacta	ctgtcaacag	agttacagaa	cttccatgta	cacttttggc	300
caggggacca	aggtggagat	caaa				324

<210> 266

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 266

Glu	Ile	Val	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Asn	Asn	Tyr
		20						25					30		
Leu	Asn	Trp	Tyr	His	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
	35						40				45				
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50				55					60					
Ser	Gly	Ser	Gly	Thr	Asp	Tyr	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70					75					80	
Glu	Asp	Phe	Gly	Asn	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Arg	Thr	Ser	Met
			85					90						95	
Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys				
			100					105							

<210> 267

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 267

cagagcatta acaactat 18

<210> 268

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 268

Gln Ser Ile Asn Asn Tyr
1 5

<210> 269

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 269

gctgcatcc 9

<210> 270

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 270

Ala Ala Ser
1

<210> 271

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 271

caacagagtt acagaacttc catgtacact 30

<210> 272

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 272

Gln	Gln	Ser	Tyr	Arg	Thr	Ser	Met	Tyr	Thr
1				5				10	

<210> 273

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 273

caggtgcagc	tgcaggagtc	gggcccagga	ctggtgaagc	cttcggagac	cctgtccctc	60
aactgcactg	tctctgggtg	ctccatcagt	acttactact	ggagctggtt	cggcagccc	120
ccagggaagg	gactggagtg	gattgggtat	atctattaca	gtgggagcac	caaccacaac	180
ccctccctca	agagtgcagt	caccatatca	gtagacacgt	ccaagaacca	gttctccctg	240
aaactgaggt	ctgtgaccgc	tgcggacacg	gocgtgtatt	actgtgcgag	agtaggtccg	300
gtgggctggg	gatcatgggg	gaactttgac	tactgggggc	agggaaccct	ggtcaccgtc	360
tectca						366

<210> 274

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 274

Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Glu
1				5					10					15	
Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile	Ser	Thr	Tyr
			20					25					30		
Tyr	Trp	Ser	Trp	Phe	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Ile
		35				40					45				
Gly	Tyr	Ile	Tyr	Tyr	Ser	Gly	Ser	Thr	Asn	His	Asn	Pro	Ser	Leu	Lys
	50				55				60						
Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys	Asn	Gln	Phe	Ser	Leu
65					70				75					80	
Lys	Leu	Arg	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
				85				90						95	
Arg	Val	Gly	Pro	Val	Gly	Trp	Gly	Ser	Trp	Gly	Asn	Phe	Asp	Tyr	Trp
			100					105					110		

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 275

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 275

ggtggctcca tcagtactta ctac 24

<210> 276

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 276

Gly Gly Ser Ile Ser Thr Tyr Tyr
 1 5

<210> 277

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 277

atctattaca gtgggagcac c 21

<210> 278

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 278

Ile Tyr Tyr Ser Gly Ser Thr
 1 5

<210> 279

<211> 48

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 279

gcgagagtag gtccggtggg ctggggatca tgggggaact ttgactac 48

<210> 280

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 280

Ala	Arg	Val	Gly	Pro	Val	Gly	Trp	Gly	Ser	Trp	Gly	Asn	Phe	Asp	Tyr
1				5				10				15			

<210> 281

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 281

gacatccagt	tgacccagtc	tccatccttc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcacttgc	gggccagtc	gggcattagc	agttatttag	cctgggtctca	gcacaaacca	120
gggaaagccc	ctaagctcct	gatctatgct	gcacccactt	tacaaagtgg	ggccccatca	180
aggttcagcg	gcagtggatc	tgggacagaa	ttcactctca	caatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ctgtcaacag	cttaatagtt	accogtggac	gttcggccaa	300
gggaccaagg	tggagatcaa	a				321

<210> 282

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 282

Asp	Ile	Gln	Leu	Thr	Gln	Ser	Pro	Ser	Phe	Leu	Ser	Ala	Ser	Val	Gly
1				5				10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Trp	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Tyr
		20						25				30			
Leu	Ala	Trp	Ser	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40				45				
Tyr	Ala	Ala	Ser	Thr	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55				60					

```

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Trp
          85          90          95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
          100          105

```

<210> 283

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 283

cagggcatta gcagttat 18

<210> 284

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 284

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Gln Gly Ile Ser Ser Tyr
1          5

```

<210> 285

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 285

gctgcatcc 9

<210> 286

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 286

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Ala Ala Ser
1

```

<210> 287

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 287

caacagctta atagttaccc gtggacg 27

<210> 288

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 288

Gln	Gln	Leu	Asn	Ser	Tyr	Pro	Trp	Thr
1			5					

<210> 289

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 289

gaggtgcagc	tgggtgcagtc	tggagctgag	gtgaagaagc	ctgggggcctc	agtgaaggtc	60
tectgcaagg	cttctgggta	cacctttacc	aattatggta	tcacctgggt	gcgacaggcc	120
cctggacaag	ggcttgagtg	gatgggggtg	atcagegctt	acaatggtaa	caccggctat	180
gcacagaaat	tcaggggcag	agtcaccatg	accacagaca	cttccacgag	cacagcctac	240
atggagctga	ggagcctgag	atctgacgac	acggccgtgt	attactgtgc	gagagaggat	300
tacgattttt	ggagggcctt	tgatatctgg	ggccaaggga	caatggtcac	cgtctcttca	360

<210> 290

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 290

Glu	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asn	Tyr
			20					25						30	

Gly	Ile	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Trp	Ile	Ser	Ala	Tyr	Asn	Gly	Asn	Thr	Gly	Tyr	Ala	Gln	Lys	Phe
	50					55				60					
Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
	65				70					75				80	
Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90					95		
Ala	Arg	Glu	Asp	Tyr	Asp	Phe	Trp	Arg	Ala	Phe	Asp	Ile	Trp	Gly	Gln
		100						105					110		
Gly	Thr	Met	Val	Thr	Val	Ser	Ser								
	115						120								

<210> 291

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 291

ggttacacct ttaccaatta tggt 24

<210> 292

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 292

Gly	Tyr	Thr	Phe	Thr	Asn	Tyr	Gly
1				5			

<210> 293

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 293

atcagcgctt acaatggtaa cacc 24

<210> 294

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 294

Ile Ser Ala Tyr Asn Gly Asn Thr
1 5

<210> 295

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 295

gcgagagagg attacgatt ttggagggt tttgatatc 39

<210> 296

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 296

Ala Arg Glu Asp Tyr Asp Phe Trp Arg Ala Phe Asp Ile
1 5 10

<210> 297

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 297

gaaattgtgc tgactcagtc tccaggaacc ctgtctttgt ctccggggga aagagccacc 60
ctctctctgca gggccagtc gagtgtagc agcacctaet tagcctgget ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac cggcatccca 180
gacaggttca gtggcagtggt gtctgggaca gacttcaetc tcaccatcaa cagactggag 240
cctgaagatt ttgcagtgtt ttattgtcaa cagtatgctt actcacgta cacttttggc 300
caggggacca agctggagat caaa 324

<210> 298

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 298

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Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Thr
          20           25           30
Tyr Leu Ala Trp Leu Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
          35           40           45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
          50           55           60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Arg Leu Glu
65           70           75           80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ala Tyr Ser Pro
          85           90           95
Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
          100          105

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<210> 299

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 299

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cagagtgtta gcagcaccta c          21

```

<210> 300

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 300

```

Gln Ser Val Ser Ser Thr Tyr
 1           5

```

<210> 301

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 301

```

ggtgcatcc          9

```

<210> 302

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 302

Gly Ala Ser

1

<210> 303

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 303

caacagtatg cttactcacc gtacact 27

<210> 304

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 304

Gln Gln Tyr Ala Tyr Ser Pro Tyr Thr
1 5

<210> 305

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 305

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cagggtgcagc tgggtggagtc tggggggaggc gtgggtccagc ctggggaggtc cctgagactc 60
tctgtgtcag cgtctggatt cagtttcagt gactatgtca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcatct atatggtttg atggaagtaa tgaattctat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa caogctgttt 240
ctgcaaataa acagtctgag agccgaggac acggctgtgt attactgtgc gaaaaaggga 300
gtgttggtag ctacctctgc ttttgatata tggggccaag ggacaatggt caccgtctct 360
tca 363

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<210> 306

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 306

```

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Tyr
      20             25             30
Val Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35             40             45
Ala Ser Ile Trp Phe Asp Gly Ser Asn Glu Phe Tyr Ala Asp Ser Val
      50             55             60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
      65             70             75             80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85             90             95
Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile Trp Gly
      100            105            110
Gln Gly Thr Met Val Thr Val Ser Ser
      115             120

```

<210> 307

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 307

ggattcagtt tcagtgacta tgtc 24

<210> 308

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 308

```

Gly Phe Ser Phe Ser Asp Tyr Val
 1             5

```

<210> 309

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 309

atatggttg atggaagtaa tgaa 24

<210> 310

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 310

Ile Trp Phe Asp Gly Ser Asn Glu
1 5

<210> 311

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 311

gcgaaaaagg gagtgttggg agctacctct gctttgata tc 42

<210> 312

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 312

Ala Lys Lys Gly Val Leu Val Ala Thr Ser Ala Phe Asp Ile
1 5 10

<210> 313

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 313

gacatccagt tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggcattaac aactatttaa attggtatca tcagaaacca 120

```

gggaaagccc ctaagctcct aatctatgct gcattccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat tacactctca ccatcagcag tctgcaacct 240
gaagattttg gaaattacta ctgtcaacag agttacagaa ctcccatgta cacttttggc 300
caggggacca aggtggaaat caaa                               324

```

<210> 314

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 314

```

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Asn Tyr
20          25          30
Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35          40          45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50          55          60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80
Glu Asp Phe Gly Asn Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Ser Met
85          90          95
Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100         105

```

<210> 315

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 315

```

cagagcatta acaactat      18

```

<210> 316

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 316

```

Gln Ser Ile Asn Asn Tyr
1           5

```

<210> 317

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 317

gctgcatcc 9

<210> 318

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 318

Ala Ala Ser

1

<210> 319

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 319

caacagagtt acagaacttc catgtacact 30

<210> 320

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 320

Gln	Gln	Ser	Tyr	Arg	Thr	Ser	Met	Tyr	Thr
1				5				10	

<210> 321

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 321

```

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc cggggggggtc cctgagaactc 60
tcctgtgcag cctctggatt caccctttagc agctatgcc a tgagctgggt ccgccaggtt 120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtgggtgataa tacatataac 180
gcagagtcgc tgaagggccg gttcaccatc tccagagaca attccaagaa tatgtttgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaaacaaaag 300
tttagcagct cgttgctctt tgactactgg ggccaggga c cctggtcac cgtctctca 360

```

<210> 322

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 322

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1           5           10           15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20           25           30
Ala Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35           40           45
Ser Ala Ile Ser Gly Ser Gly Asp Asn Thr Tyr Asn Ala Glu Ser Val
50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Met Leu Tyr
65           70           75           80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85           90           95
Ala Lys Thr Lys Phe Ser Ser Ser Leu Leu Phe Asp Tyr Trp Gly Gln
100          105          110
Gly Thr Leu Val Thr Val Ser Ser
115          120

```

<210> 323

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 323

```

ggattcacct ttagcagcta tgcc          24

```

<210> 324

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 324

Gly Phe Thr Phe Ser Ser Tyr Ala
 1 5

<210> 325

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 325

attagtggta gtggtgataa taca 24

<210> 326

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 326

Ile Ser Gly Ser Gly Asp Asn Thr
 1 5

<210> 327

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 327

gcgaaaacaa agttagcag ctcgttgctc ttgactac 39

<210> 328

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 328

Ala Lys Thr Lys Phe Ser Ser Ser Leu Leu Phe Asp Tyr
 1 5 10

<210> 329

<211> 318

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 329

```

gacatcgtga tgaccacgtc tccctccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt tgggtggttg cctgggtatc gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gogtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tataatagtt attccacttt cggcggaggg 300
accaagctgg agatcaaa                                     318

```

<210> 330

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 330

```

Asp Ile Val Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1              5              10              15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Trp Trp

                20                25                30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35              40              45
Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50              55              60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65              70              75              80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Ser Thr
                85              90              95
Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100              105

```

<210> 331

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 331

```

cagagtatta gttggtgg          18

```

<210> 332

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 332

Gln Ser Ile Ser Trp Trp
1 5

<210> 333

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 333

aaggcgtct 9

<210> 334

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 334

Lys Ala Ser

1

<210> 335

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 335

caacagtata atagttattc cact 24

<210> 336

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 336

Gln Gln Tyr Asn Ser Tyr Ser Thr
 1 5

<210> 337

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 337

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
 tctgtgtcag cctctacatt cacccttttagc agctatgccg tgacctgggt ccgccaggct 120
 ccagggaagg ggctggagtg ggtctcaagt attagtggta gtggtgatag cacatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgttt 240
 ctgcaaataa acagcctgag agccgaggac acggccgtat attactgtgc gaaaaaggat 300
 gggcctggga ggtattacgt gaggtacggt atggacgtct ggggcccaagg gaccacggtc 360
 accgtctcct ca 372

<210> 338

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 338

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Thr Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Lys Asp Gly Pro Gly Arg Tyr Tyr Val Arg Tyr Gly Met Asp
 100 105 110
 Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 339

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 339

acattcacct ttagcagcta tgcc 24

<210> 340

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 340

Thr Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 341

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 341

attagtggta gtggtgatag caca 24

<210> 342

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 342

Ile Ser Gly Ser Gly Asp Ser Thr
1 5

<210> 343

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 343

gcgaaaaagg atgggcctgg gaggtattac gtgaggtacg gtatggacgt c 51

<210> 344

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 344

Ala	Lys	Lys	Asp	Gly	Pro	Gly	Arg	Tyr	Tyr	Val	Arg	Tyr	Gly	Met	Asp
1				5				10					15		
Val															

<210> 345

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 345

gacatccaga	tgacccagtc	tccatcttcc	gtgtctgcat	ctgtaggaga	cagagtcacc	60
atcaattgtc	gggagagtc	gggtattagc	agctgggttag	cctgggtatca	gcagaaacca	120
gggaaagccc	ctaagctcct	gatctatact	acatccagtt	tgcaaagtgg	ggtcccatcc	180
aggttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ttgtcaacag	gctaacagtt	tccctctcac	tttcggcgga	300
gggaccaaaag	tgatatcaaa	a				321

<210> 346

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 346

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5				10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp
		20						25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
	35						40				45				
Tyr	Thr	Thr	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50				55					60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ala	Asn	Ser	Phe	Pro	Leu
			85					90						95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Asp	Ile	Lys					
			100					105							

<210> 347
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 347
 cagggattta gcagctgg 18

<210> 348
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 348
 Gln Gly Ile Ser Ser Trp
 1 5

<210> 349
 <211> 9
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 349
 actacatcc 9

<210> 350
 <211> 3
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 350
 Thr Thr Ser
 1

<210> 351
 <211> 27
 <212> DNA
 <213> Artificial Sequence

<220>

<223> Synthetic

<400> 351

caacaggcta acagtttccc tctcact 27

<210> 352

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 352

Gln	Gln	Ala	Asn	Ser	Phe	Pro	Leu	Thr
1				5				

<210> 353

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 353

gaggtgcagc	tggtggagtc	tgggggaggc	ttggaacagc	ctgggggggtc	cctgagactc	60
tctgtgtcag	cctctggatt	caccttttagc	agctatgtca	tgagctgggt	ccgccagggt	120
ccagggaagg	ggctggagtg	ggtctcagtt	atcagtggtg	gtgggtggtag	cacatactac	180
gcagactccg	tgaagggccg	gttcaccatc	tcagagaca	attccaagaa	cacgctgtat	240
ctgcaaatga	acagcctgag	agccgaggac	acggccgtat	attactgtgc	gaaaccctca	300
tcttatagca	gctcgaaact	ccactacggg	atggacgtct	ggggccaagg	gaccacggtc	360
accgtctcct	ca					372

<210> 354

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 354

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Glu	Gln	Pro	Gly	Gly
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
			20					25					30		
Val	Met	Ser	Trp	Val	Arg	Gln	Val	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Val	Ile	Ser	Gly	Ser	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Ile	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Ile	Asp	Thr	Leu	Tyr

```

Lys Gly Arg Phe Ile Ile Ser Arg Asp Asn Ser Lys Asn Thr Ser Lys
65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85          90          95
Ala Lys Pro Ser Ser Tyr Ser Ser Ser Asn Phe His Tyr Gly Met Asp
      100        105        110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120

```

<210> 355

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 355

ggattcacct ttagcagcta tgct 24

<210> 356

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 356

```

Gly Phe Thr Phe Ser Ser Tyr Val
1          5

```

<210> 357

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 357

atcagtggta gtggtgtag caca 24

<210> 358

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 358

Ile Ser Gly Ser Gly Gly Ser Thr

1 5 "

<210> 359

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 359

gcgaaaccct catcttatag cagctcgaac ttccactacg gtatggacgt c 51

<210> 360

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 360

Ala	Lys	Pro	Ser	Ser	Tyr	Ser	Ser	Ser	Asn	Phe	His	Tyr	Gly	Met	Asp
1				5				10						15	
Val															

<210> 361

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 361

```

gacatccaga tgacccagtc tocatattcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcaettgtc gggcgagtcg ggggtattag agctggttag cctggatatc gcagaaacca 120
gggagagccc ctaagctcct gatctatgct gcattccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcaactctc ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaaaag actaacagtt tccattcac tttcggccct 300
gggaccaagg tggaaatcaa a                                     321

```

<210> 362

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 362

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Tyr	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5				10					15		

```

      1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
      20           25           30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Ile

      35           40           45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
      50           55           60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65           70           75           80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Lys Thr Asn Ser Phe Pro Phe
      85           90           95
Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
      100           105

```

<210> 363

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 363

cagggtatta gcagctgg 18

<210> 364

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 364

```

Gln Gly Ile Ser Ser Trp
 1           5

```

<210> 365

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 365

gctgcatcc 9

<210> 366

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 366

Ala Ala Ser
1

<210> 367

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 367

caaaagacta acagtttccc attcact 27

<210> 368

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 368

Gln Lys Thr Asn Ser Phe Pro Phe Thr
1 5

<210> 369

<211> 141

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 369

Ala	Gly	Gly	Pro	Gly	Ser	Arg	Ala	Arg	Ala	Ala	Gly	Ala	Arg	Gly	Cys
1				5					10					15	
Arg	Leu	Arg	Ser	Gln	Leu	Val	Pro	Val	Arg	Ala	Leu	Gly	Leu	Gly	His
			20					25					30		
Arg	Ser	Asp	Glu	Leu	Val	Arg	Phe	Arg	Phe	Cys	Ser	Gly	Ser	Cys	Arg
		35					40					45			
Arg	Ala	Arg	Ser	Pro	His	Asp	Leu	Ser	Leu	Ala	Ser	Leu	Leu	Gly	Ala
	50					55					60				
Gly	Ala	Leu	Arg	Pro	Pro	Gly	Ser	Arg	Pro	Val	Ser	Gln	Pro	Cys	
65					70				75					80	
Cys	Arg	Pro	Thr	Arg	Tyr	Glu	Ala	Val	Ser	Phe	Met	Asp	Val	Asn	Ser
				85					90					95	
Thr	Trp	Arg	Thr	Val	Asp	Arg	Leu	Ser	Ala	Thr	Ala	Cys	Gly	Cys	Leu
			100					105					110		
Gly	Glu	Gln	Lys	Leu	Ile	Ser	Glu	Glu	Asp	Leu	Gly	Gly	Glu	Gln	Lys
		115					120					125			

¹¹⁰
 Leu Ile Ser Glu Glu Asp Leu ¹²⁰ His His His His His ¹²⁵ His
 130 135 140

<210> 370

<211> 371

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 370

Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala
 1 5 10 15
 Arg Arg Lys Cys Gln Ala Asp Pro Thr Cys Ser Ala Ala Tyr His His
 20 25 30
 Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu
 35 40 45
 Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn
 50 55 60
 Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val
 65 70 75 80
 Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly
 85 90 95
 Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
 100 105 110
 Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
 115 120 125
 Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys
 130 135 140
 Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys
 145 150 155 160
 Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala
 165 170 175
 Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn
 180 185 190
 Asp Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Asn Cys
 195 200 205
 Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys
 210 215 220
 Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His
 225 230 235 240
 Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
 245 250 255
 Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
 260 265 270
 Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg
 275 280 285
 Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Met Leu Glu Gly Phe Phe
 290 295 300
 Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Lys Met Arg Phe
 305 310 315 320
 His Ser Gln Leu Phe Ser Gln Asp Trp Pro His Pro Thr Phe Ala Val
 325 330 335
 Met Ala His Gln Asn Glu Asn Glu Gln Lys Leu Ile Ser Glu Glu Asp
 340 345 350
 Leu Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu His His His
 355 360 365
 His His His
 370

<210> 371

<211> 578

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 371

```

Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala
 1          5          10          15
Arg Arg Lys Cys Gln Ala Asp Pro Thr Cys Ser Ala Ala Tyr His His
 20          25          30
Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu
 35          40          45
Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn
 50          55          60
Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val
 65          70          75          80
Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly
 85          90          95
Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
100          105          110
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
115          120          125
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys
130          135          140
Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys
145          150          155          160
Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala
165          170          175
Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn
180          185          190
Asp Arg Gly Cys Gly Glu Arg Arg Asn Thr Ile Ala Pro Asn Cys
195          200          205
Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys
210          215          220
Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His
225          230          235          240
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
245          250          255
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
260          265          270
Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg
275          280          285
Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Met Leu Glu Gly Phe Phe
290          295          300
Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala Lys Met Arg Phe
305          310          315          320
His Ser Gln Leu Phe Ser Gln Asp Trp Pro His Pro Thr Phe Ala Val
325          330          335
Met Ala His Gln Asn Glu Asn Pro Ala Val Arg Pro Gln Pro Trp Asp
340          345          350
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
355          360          365
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
370          375          380
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
385          390          395          400
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
405          410          415

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
420          425          430
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
435          440          445
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
450          455          460

```

450	Lys Thr Ile Ser Lys Ala	455	Lys Gly Gln Pro Arg	460	Glu Pro Gln Val Tyr
465	Thr Leu Pro Pro Ser Arg	470	Asp Glu Leu Thr Lys	475	Asn Gln Val Ser Leu
	485		490		495
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp			505		510
	500		520		525
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val					
	515				
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp					
	530		535		540
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His					560
	545		550		555
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro			570		575
	565				
Gly Lys					

<210> 372

<211> 584

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 372

Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala		
1	5	10
Arg Arg Lys Cys Gln Ala Asp Pro Thr Cys Ser Ala Ala Tyr His His		
	20	25
Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu		
	35	40
Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn		
	50	55
Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val		
	65	70
Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly		
	85	90
Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys		
	100	105
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser		
	115	120
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys		
	130	135
Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys		
	145	150
Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala		
	165	170
Ala Glu Pro His Ala Gln Gly Leu Leu Cys Pro Cys Ala Pro Asn		
	180	185
Asp Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Asn Cys		
	195	200
Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys		
	210	215
Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His		
	225	230
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg		
	245	250
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn		
	260	265
Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg		
	275	280
Gly Ser Gly Asn Leu Gln Glu Cys Glu Met Leu Glu Gly Phe Phe		
	290	295
		300

```

    220      220      220
Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala Lys Met Arg Phe
305      310      315      320
His Ser Gln Leu Phe Ser Gln Asp Trp Pro His Pro Thr Phe Ala Val
      325      330      335
Met Ala His Gln Asn Glu Asn Pro Ala Val Arg Pro Gln Pro Trp Glu
      340      345      350
Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala
      355      360      365
Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile
      370      375      380
Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val
385      390      395      400
Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val
      405      410      415
Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp
      420      425      430
Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln
      435      440      445
Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp
      450      455      460
Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val
465      470      475      480
Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr
      485      490      495
Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu
      500      505      510
Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr
      515      520      525
Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr
      530      535      540
Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr
545      550      555      560
Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys
      565      570      575
Ser Phe Ser Arg Thr Pro Gly Lys
      580

```

<210> 373

<211> 371

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 373

```

Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala
1      5      10      15
Arg Arg Lys Cys Gln Ala Asp Pro Ile Cys Ser Ala Ala Tyr His His
      20      25      30
Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu
      35      40      45
Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn
      50      55      60
Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val
65      70      75      80
Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly
      85      90      95
Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
      100      105      110
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
      115      120      125
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys
130      135      140
Asn Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys

```

```

Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Phe His Cys
145      150      155      160
Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala
      165      170      175
Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn
      180      185      190
Asp Arg Gly Cys Gly Glu Arg Arg Asn Thr Ile Ala Pro Ser Cys
      195      200      205
Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys
      210      215      220
Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His
225      230      235      240
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
      245      250      255
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
      260      265      270
Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg
      275      280      285
Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Gln Leu Glu Gly Phe Phe
      290      295      300
Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Lys Met Arg Phe
305      310      315      320
His Ser Gln Leu Phe Tyr Gln Asp Trp Pro His Pro Thr Phe Ala Val
      325      330      335
Met Ala His Gln Asn Glu Asn Glu Gln Lys Leu Ile Ser Glu Glu Asp
      340      345      350
Leu Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu His His His
      355      360      365
His His His
      370

```

<210> 374

<211> 1200

<212> DNA

<213> Homo sapiens

<400> 374

```

atggtgcgcc cctgaaccc ggcaccgtg cgcgccgtg tctgatgtt gctgctgctg 60
ctgccgcgct cgcgcgtgcc tctgcagcc ggagacccc ttcccacaga aagccgactc 120
atgaacagct gtctccaggc caggaggaag tgccaggctg atcccacctg cagtgcctgc 180
taccaccacc tggattcctg cacctctagc ataagcacc cactgccctc agaggagcct 240
tcgggtccctg ctgactgctt ggaggcagca cagcaactca ggaacagctc tctgataggc 300
tgcatgtgcc accggcgcat gaagaaccag gttgcctgct tggacatcta ttggaccgtt 360
cacctgtccc gcagccttgg taactatgag ctggatgtct cccctatga agacacagt 420
accagcaaac cctggaaaat gaatctcagc aaactgaaca tgctcaaacc agactcagac 480
ctctgcctca agtttgccat gctgtgtact ctcaatgaca agtgtgaccg gctgcgcaag 540
gcctacgggg aggcgtgctc cgggccccac tgcagcgcc acgtctgcct caggcagctg 600
ctcactttct tcgagaaggc cgcgcgccc cgcgcgagg gcctgctact gtgcccatgt 660
gcccccaacg accggggctg cggggagcgc cggcgcaaca ccacgcgcc caactgcgcg 720
ctgcgcctg tggcccccaa ctgcctggag ctgcggcgcc tctgcttctc cgaccgcctt 780
tgccagatcac gcctggtgga ttccagacc cactgccatc ccattggacat cctaggaact 840
tgtgcaacag agcagtcacg atgtctacga gcatacctg ggctgattgg gactgccatg 900
acccccaaat ttgtcagcaa tgtcaacacc agtgttgct taagctgcac ctgcgagggc 960
agtggcaacc tgcaggagga gtgtgaaatg ctggaagggt tcttctccca caacctctgc 1020
ctcacggagg ccattgcagc taagatgcgt ttccacagcc aactcttctc ccaggactgg 1080
ccacacccta cctttgctgt gatggcacac cagaatgaaa accctgctgt gaggccacag 1140
ccctgggtgc cctctctttt ctctgcacg ctcccttga ttctgctct gaggcctatgg 1200

```

<210> 375

<211> 400

<212> PRT

<213> Homo sapiens

<400> 375

```

Met Val Arg Pro Leu Asn Pro Arg Pro Leu Pro Pro Val Val Leu Met
 1          5          10          15
Leu Leu Leu Leu Leu Pro Pro Ser Pro Leu Pro Leu Ala Ala Gly Asp
 20          25          30
Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser Cys Leu Gln Ala Arg
 35          40          45
Arg Lys Cys Gln Ala Asp Pro Thr Cys Ser Ala Ala Tyr His His Leu
 50          55          60
Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu Pro Ser Glu Glu Pro
 65          70          75          80
Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln Gln Leu Arg Asn Ser
 85          90          95
Ser Leu Ile Gly Cys Met Cys His Arg Arg Met Lys Asn Gln Val Ala
100          105          110
Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala Arg Ser Leu Gly Asn
115          120          125
Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys Pro
130          135          140
Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser Asp
145          150          155          160
Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu Asn Asp Lys Cys Asp
165          170          175
Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Pro His Cys Gln
180          185          190
Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe Phe Glu Lys Ala Ala
195          200          205
Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Asn Asp
210          215          220
Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Asn Cys Ala
225          230          235          240

Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu Arg Arg Leu Cys Phe
245          250          255
Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp Phe Gln Thr His Cys
260          265          270
His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg Cys
275          280          285
Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn Phe
290          295          300
Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser Cys Thr Cys Arg Gly
305          310          315          320
Ser Gly Asn Leu Gln Glu Glu Cys Glu Met Leu Glu Gly Phe Phe Ser
325          330          335
His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala Lys Met Arg Phe His
340          345          350
Ser Gln Leu Phe Ser Gln Asp Trp Pro His Pro Thr Phe Ala Val Met
355          360          365
Ala His Gln Asn Glu Asn Pro Ala Val Arg Pro Gln Pro Trp Val Pro
370          375          380
Ser Leu Phe Ser Cys Thr Leu Pro Leu Ile Leu Leu Leu Ser Leu Trp
385          390          395          400

```

<210> 376

<211> 632

<212> PRT

<213> Homo sapiens

<400> 376

```

Asp Arg Leu Asp Cys Val Lys Ala Ser Asp Gln Cys Leu Lys Glu Gln
 1          5          10          15
Ser Cys Ser Thr Lys Tyr Arg Thr Leu Arg Gln Cys Val Ala Gly Lys
 20          25          30
Glu Thr Asn Phe Ser Leu Ala Ser Gly Leu Glu Ala Lys Asp Glu Cys
 35          40          45

```

Arg	Ser	Ala	Met	Glu	Ala	Leu	Lys	Gln	Lys	Ser	Leu	Tyr	Asn	Cys	Arg
50						55					60				
Cys	Lys	Arg	Gly	Met	Lys	Lys	Glu	Lys	Asn	Cys	Leu	Arg	Ile	Tyr	Trp
65					70				75						80
Ser	Met	Tyr	Gln	Ser	Leu	Gln	Gly	Asn	Asp	Leu	Leu	Glu	Asp	Ser	Pro
			85					90						95	
Tyr	Glu	Pro	Val	Asn	Ser	Arg	Leu	Ser	Asp	Ile	Phe	Arg	Val	Val	Pro
			100					105					110		
Phe	Ile	Ser	Asp	Val	Phe	Gln	Gln	Val	Glu	His	Ile	Pro	Lys	Gly	Asn
		115					120					125			
Asn	Cys	Leu	Asp	Ala	Ala	Lys	Ala	Cys	Asn	Leu	Asp	Asp	Ile	Cys	Lys
		130				135					140				
Lys	Tyr	Arg	Ser	Ala	Tyr	Ile	Thr	Pro	Cys	Thr	Thr	Ser	Val	Ser	Asn
145					150					155					160
Asp	Val	Cys	Asn	Arg	Arg	Lys	Cys	His	Lys	Ala	Leu	Arg	Gln	Phe	Phe
			165					170						175	
Asp	Lys	Val	Pro	Ala	Lys	His	Ser	Tyr	Gly	Met	Leu	Phe	Cys	Ser	Cys
			180					185					190		
Arg	Asp	Ile	Ala	Cys	Thr	Glu	Arg	Arg	Arg	Gln	Thr	Ile	Val	Pro	Val
		195				200						205			
Cys	Ser	Tyr	Glu	Glu	Arg	Glu	Lys	Pro	Asn	Cys	Leu	Asn	Leu	Gln	Asp
		210				215					220				
Ser	Cys	Lys	Thr	Asn	Tyr	Ile	Cys	Arg	Ser	Arg	Leu	Ala	Asp	Phe	Phe
225					230					235					240
Thr	Asn	Cys	Gln	Pro	Glu	Ser	Arg	Ser	Val	Ser	Ser	Cys	Leu	Lys	Glu
				245					250					255	
Asn	Tyr	Ala	Asp	Cys	Leu	Leu	Ala	Tyr	Ser	Gly	Leu	Ile	Gly	Thr	Val
		260						265					270		
Met	Thr	Pro	Asn	Tyr	Ile	Asp	Ser	Ser	Ser	Leu	Ser	Val	Ala	Pro	Trp
		275					280					285			
Cys	Asp	Cys	Ser	Asn	Ser	Gly	Asn	Asp	Leu	Glu	Glu	Cys	Leu	Lys	Phe
		290				295					300				
Leu	Asn	Phe	Phe	Lys	Asp	Asn	Thr	Cys	Leu	Lys	Asn	Ala	Ile	Gln	Ala
305					310					315					320
Phe	Gly	Asn	Gly	Ser	Asp	Val	Thr	Val	Trp	Gln	Pro	Ala	Phe	Pro	Val
			325						330					335	
Gln	Thr	Thr	Thr	Ala	Thr	Thr	Thr	Thr	Ala	Leu	Arg	Val	Lys	Asn	Lys
			340					345					350		
Pro	Leu	Gly	Pro	Ala	Gly	Ser	Glu	Asn	Glu	Ile	Pro	Thr	His	Val	Leu
		355					360					365			
Pro	Pro	Cys	Ala	Asn	Leu	Gln	Ala	Gln	Lys	Leu	Lys	Ser	Asn	Val	Ser
		370				375					380				
Gly	Asn	Thr	His	Leu	Cys	Ile	Ser	Asn	Gly	Asn	Tyr	Glu	Lys	Glu	Gly
385					390				395						400
Leu	Gly	Ala	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala
			405					410					415		
Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro
			420					425					430		
Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
		435				440						445			
Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val
		450				455					460				
Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln
465					470					475					480
Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln
			485					490						495	
Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala
			500					505					510		
Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro
		515					520					525			
Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr
		530				535					540				
Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
545					550					555					560
Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr
			565					570					575		
Lys	Thr	Thr	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	
			580				585					590			

```

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
595                      600                      605
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
610                      615                      620
Ser Leu Ser Leu Ser Pro Gly Lys
625                      630

```

<210> 377

<211> 405

<212> PRT

<213> Artificial Sequence

<220>

<223> Cynomolgus GFRalpha3: cerebellum cDNA

<400> 377

```

Met Val Arg Pro Pro Ser Pro Arg Pro Leu Pro Pro Val Val Leu Met
1      5      10
Leu Leu Leu Leu Leu Leu Leu Leu Pro Pro Ser Pro Leu Pro
20     25     30
Leu Ala Ala Gly Asp Pro Leu Pro Thr Glu Ser Arg Leu Met Asn Ser
35     40     45
Cys Leu Gln Ala Arg Arg Lys Cys Gln Ala Asp Pro Ile Cys Ser Ala
50     55     60
Ala Tyr His His Leu Asp Ser Cys Thr Ser Ser Ile Ser Thr Pro Leu
65     70     75     80
Pro Ser Glu Glu Pro Ser Val Pro Ala Asp Cys Leu Glu Ala Ala Gln
85     90     95
Gln Leu Arg Asn Ser Ser Leu Ile Gly Cys Met Cys His Arg Arg Met
100    105    110
Lys Asn Gln Val Ala Cys Leu Asp Ile Tyr Trp Thr Val His Arg Ala
115    120    125
Arg Ser Leu Gly Asn Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr
130    135    140
Val Thr Ser Lys Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu
145    150    155    160
Lys Pro Asp Ser Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu
165    170    175
Asn Asp Lys Cys Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser
180    185    190
Gly Pro His Cys Gln Arg His Val Cys Leu Arg Gln Leu Leu Thr Phe
195    200    205
Phe Glu Lys Ala Ala Glu Pro His Ala Gln Gly Leu Leu Leu Cys Pro
210    215    220
Cys Ala Pro Asn Asp Arg Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile
225    230    235    240
Ala Pro Ser Cys Ala Leu Pro Pro Val Ala Pro Asn Cys Leu Glu Leu
245    250    255
Arg Arg Leu Cys Phe Ser Asp Pro Leu Cys Arg Ser Arg Leu Val Asp
260    265    270
Phe Gln Thr His Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr
275    280    285
Glu Gln Ser Arg Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala
290    295    300
Met Thr Pro Asn Phe Val Ser Asn Val Asn Thr Ser Val Ala Leu Ser
305    310    315    320
Cys Thr Cys Arg Gly Ser Gly Asn Leu Gln Glu Glu Cys Glu Gln Leu
325    330    335
Glu Gly Phe Phe Ser His Asn Pro Cys Leu Thr Glu Ala Ile Ala Ala
340    345    350
Lys Met Arg Phe His Ser Gln Leu Phe Tyr Gln Asp Trp Pro His Pro
355    360    365
Thr Phe Ala Val Met Ala His Gln Asn Glu Asn Arg Ala Leu Arg Ser
370    375    380

```

Lys Pro Trp Ala Pro Ser Leu Phe Ser Cys Thr Leu Pro Leu Ile Leu
 385 390 395 400
 Leu Leu Ser Leu Trp
 405

<210> 378

<211> 1086

<212> PRT

<213> Artificial Sequence

<220>

<223> Cynomolgus RET without signal sequence

<400> 378

Leu Tyr Phe Ser Arg Asp Ala Tyr Trp Glu Lys Leu Tyr Val Asp Gln
 1 5 10 15
 Pro Ala Gly Thr Pro Leu Leu Tyr Val His Ala Leu Arg Asp Ala Pro
 20 25 30
 Glu Glu Val Pro Ser Phe Arg Leu Gly Gln His Leu Tyr Gly Thr Tyr
 35 40 45
 Arg Thr Arg Leu His Glu Asn Asn Trp Ile Cys Ile Gln Glu Asp Thr
 50 55 60
 Gly Leu Leu Tyr Leu Asn Arg Ser Leu Asp Arg Ser Ser Trp Glu Lys
 65 70 75 80
 Leu Ser Gly Arg Asn Arg Gly Phe Pro Leu Leu Thr Val Tyr Leu Lys
 85 90 95
 Val Phe Leu Ser Pro Thr Ser Leu Arg Glu Gly Glu Cys Gln Trp Pro
 100 105 110
 Gly Cys Ala Arg Val Tyr Phe Ser Phe Phe Asn Thr Ser Phe Pro Ala
 115 120 125
 Cys Thr Ser Leu Lys Pro Arg Glu Leu Cys Phe Pro Glu Thr Arg Pro
 130 135 140
 Ser Phe Arg Ile Arg Glu Asn Arg Pro Pro Gly Thr Phe His Gln Phe
 145 150 155 160
 Arg Leu Leu Pro Val Gln Phe Leu Cys Pro Asn Ile Ser Val Ala Tyr
 165 170 175
 Arg Leu Leu Glu Gly Glu Gly Leu Pro Phe Arg Cys Ala Pro Asp Ser
 180 185 190
 Leu Glu Val Ser Thr Arg Trp Ala Leu Asp Arg Glu Gln Arg Glu Lys
 195 200 205
 Tyr Glu Leu Val Ala Val Cys Thr Val His Ala Gly Ala Arg Glu Glu
 210 215 220
 Val Val Met Val Pro Phe Pro Val Thr Val Tyr Asp Glu Asp Asp Ser
 225 230 235 240
 Ala Pro Thr Phe Pro Ala Gly Val Asp Thr Ala Ser Ala Val Val Glu
 245 250 255
 Phe Lys Arg Lys Glu Asp Thr Val Val Ala Thr Leu Arg Val Phe Asp
 260 265 270
 Ala Asp Val Val Pro Ala Ser Gly Glu Leu Val Arg Arg Tyr Thr Ser
 275 280 285
 Thr Leu Leu Pro Gly Asp Thr Trp Thr Gln Gln Thr Phe Arg Val Glu
 290 295 300
 His Trp Pro Asn Glu Thr Ser Val Gln Ala Asn Gly Ser Phe Val Arg
 305 310 315 320
 Ala Thr Val His Asp Tyr Arg Leu Val Leu Asn Arg Asn Leu Ser Ile
 325 330 335
 Ser Glu Asn Arg Thr Met Gln Leu Ala Val Leu Val Asn Asp Ser Asp
 340 345 350
 Phe Gln Gly Pro Gly Ala Gly Val Leu Leu Leu His Phe Asn Val Ser
 355 360 365
 Val Leu Pro Val Ser Leu His Leu Pro Ser Ser Tyr Ser Leu Ser Val
 370 375 380
 Ser Arg Arg Ala Arg Arg Phe Ala Gln Ile Gly Lys Val Cys Val Glu
 385 390 395 400

```

Asn Cys Gln Ala Phe Ser Gly Ile Asn Val Gln Tyr Glu Leu His Ser
      405      410      415
Ser Gly Ala Asn Cys Ser Thr Leu Gly Val Val Thr Ser Ala Glu Asp
      420      425      430
Thr Ser Gly Ile Leu Phe Val Asn Asp Thr Lys Ala Leu Arg Arg Pro
      435      440      445
Lys Cys Ala Glu Leu His Tyr Met Val Val Ala Thr Asn His Gln Thr
      450      455      460
Ser Arg Gln Ala Gln Ala Gln Leu Leu Val Thr Val Glu Gly Leu Tyr
465      470      475      480
Val Ala Glu Glu Ala Gly Cys Pro Leu Ser Cys Ala Val Ser Lys Arg
      485      490      495
Arg Pro Glu Cys Glu Glu Cys Gly Gly Leu Gly Ser Pro Thr Gly Arg
      500      505      510
Cys Glu Trp Arg Gln Gly Asp Gly Lys Gly Ile Thr Arg Asn Phe Ser
      515      520      525
Thr Cys Ser Pro Ser Thr Lys Thr Cys Pro Asp Gly His Cys Asp Val
      530      535      540
Val Glu Thr Gln Asp Ile Asn Ile Cys Pro Gln Asp Cys Leu Arg Gly
545      550      555      560
Ser Ile Val Gly Gly His Glu Pro Gly Glu Pro Arg Gly Ile Lys Ala
      565      570      575
Gly Tyr Gly Thr Cys Asn Cys Phe Pro Glu Glu Glu Lys Cys Phe Cys
      580      585      590
Glu Pro Glu Asp Ile Gln Asp Pro Leu Cys Asp Glu Leu Cys Arg Thr
      595      600      605
Val Ile Ala Ala Ala Val Leu Phe Ser Phe Ile Val Ser Val Leu Leu
      610      615      620
Ser Ala Phe Cys Ile His Arg Tyr His Lys Phe Ala His Lys Pro Pro
625      630      635      640
Ile Pro Ser Ala Glu Met Thr Phe Arg Arg Pro Ala Gln Ala Phe Pro
      645      650      655
Val Ser Tyr Ser Ser Ser Gly Ala Arg Arg Pro Ser Leu Asp Ser Met
      660      665      670
Glu Asn Gln Val Ser Val Asp Ala Phe Lys Ile Pro Glu Asp Pro Lys
      675      680      685
Trp Glu Phe Pro Arg Lys Asn Leu Val Leu Gly Lys Thr Leu Gly Glu
      690      695      700
Gly Glu Phe Gly Lys Val Val Lys Ala Thr Ala Phe Arg Leu Lys Gly
705      710      715      720
Arg Ala Gly Tyr Thr Thr Val Ala Val Lys Met Leu Lys Glu Asn Ala
      725      730      735
Ser Pro Ser Glu Leu Arg Asp Leu Leu Ser Glu Phe Asn Leu Leu Lys
      740      745      750
Gln Val Asn His Pro His Val Ile Lys Leu Tyr Gly Ala Cys Ser Gln
      755      760      765
Asp Gly Pro Leu Leu Leu Ile Val Glu Tyr Ala Lys Tyr Gly Ser Leu
      770      775      780
Arg Gly Phe Leu Arg Glu Ser Arg Lys Val Gly Pro Gly Tyr Leu Gly
785      790      795      800
Ser Gly Gly Ser Arg Asn Ser Ser Ser Leu Asp His Pro Asp Glu Arg
      805      810      815
Ala Leu Thr Met Gly Asp Leu Ile Ser Phe Ala Trp Gln Ile Ser Arg
      820      825      830
Gly Met Gln Tyr Leu Ala Glu Met Lys Leu Val His Arg Asp Leu Ala
      835      840      845
Ala Arg Asn Ile Leu Val Ala Glu Gly Arg Lys Met Lys Ile Ser Asp
      850      855      860

Phe Gly Leu Ser Arg Asp Val Tyr Glu Glu Asp Ser Tyr Val Lys Arg
865      870      875      880
Ser Lys Gly Arg Ile Pro Val Lys Trp Met Ala Ile Glu Ser Leu Phe
      885      890      895
Asp His Ile Tyr Thr Thr Gln Ser Asp Val Trp Ser Phe Gly Val Leu
      900      905      910
Leu Trp Glu Ile Val Thr Leu Gly Gly Asn Pro Tyr Pro Gly Ile Pro
      915      920      925
Pro Glu Arg Leu Phe Asn Leu Leu Lys Thr Gly His Arg Met Glu Arg
      930      935      940
Pro Asp Asn Cys Ser Glu Glu Met Tyr Arg Leu Met Leu Gln Cys Trp
845      850      855      860

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940          950          960          970
Lys Gln Glu Pro Asp Lys Arg Pro Val Phe Ala Asp Ile Ser Lys Asp
          965          970          975
Leu Glu Lys Met Met Val Lys Ser Arg Asp Tyr Leu Asp Leu Ala Ala
          980          985          990
Ser Thr Pro Ser Asp Ser Leu Leu Tyr Asp Asp Gly Leu Ser Glu Glu
          995          1000          1005
Glu Thr Pro Leu Val Asp Cys Asn Asn Ala Pro Leu Pro Arg Ala Leu
          1010          1015          1020
Pro Ser Thr Trp Ile Glu Asn Lys Leu Tyr Gly Met Ser Asp Pro Asn
          1025          1030          1035          1040
Trp Pro Gly Glu Ser Pro Val Pro Leu Thr Arg Ala Asp Gly Thr Asn
          1045          1050          1055
Thr Gly Phe Pro Arg Tyr Ala Asn Asp Ser Val Tyr Ala Asn Trp Met
          1060          1065          1070
Leu Ser Pro Ser Ala Ala Lys Leu Met Asp Thr Phe Asp Ser
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<400> 379

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Arg Lys Lys Cys Glu Ala Asn Pro Ala Cys Lys Ala Ala Tyr Gln His
20     25     30
Leu Gly Ser Cys Thr Ser Ser Leu Ser Arg Pro Leu Pro Leu Glu Glu
35     40     45
Ser Ala Met Ser Ala Asp Cys Leu Glu Ala Ala Glu Gln Leu Arg Asn
50     55     60
Ser Ser Leu Ile Asp Cys Arg Cys His Arg Arg Met Lys His Gln Ala
65     70     75     80
Thr Cys Leu Asp Ile Tyr Trp Thr Val His Pro Ala Arg Ser Leu Gly
85     90     95
Asp Tyr Glu Leu Asp Val Ser Pro Tyr Glu Asp Thr Val Thr Ser Lys
100    105    110
Pro Trp Lys Met Asn Leu Ser Lys Leu Asn Met Leu Lys Pro Asp Ser
115    120    125
Asp Leu Cys Leu Lys Phe Ala Met Leu Cys Thr Leu His Asp Lys Cys

130          135          140
Asp Arg Leu Arg Lys Ala Tyr Gly Glu Ala Cys Ser Gly Ile Arg Cys
145          150          155          160
Gln Arg His Leu Cys Leu Ala Gln Leu Arg Ser Phe Phe Glu Lys Ala
165          170          175
Ala Glu Ser His Ala Gln Gly Leu Leu Leu Cys Pro Cys Ala Pro Glu
180          185          190
Asp Ala Gly Cys Gly Glu Arg Arg Arg Asn Thr Ile Ala Pro Ser Cys
195          200          205
Ala Leu Pro Ser Val Thr Pro Asn Cys Leu Asp Leu Arg Ser Phe Cys
210          215          220
Arg Ala Asp Pro Leu Cys Arg Ser Arg Leu Met Asp Phe Gln Thr His
225          230          235          240
Cys His Pro Met Asp Ile Leu Gly Thr Cys Ala Thr Glu Gln Ser Arg
245          250          255
Cys Leu Arg Ala Tyr Leu Gly Leu Ile Gly Thr Ala Met Thr Pro Asn
260          265          270
Phe Ile Ser Lys Val Asn Thr Thr Val Ala Leu Ser Cys Ser Cys Arg

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	275					280						285							
Gly	Ser	Gly	Asn	Leu	Gln	Asp	Glu	Cys	Glu	Gln	Leu	Glu	Arg	Ser	Phe				
	290					295					300								
Ser	Gln	Asn	Pro	Cys	Leu	Val	Glu	Ala	Ile	Ala	Ala	Lys	Met	Arg	Phe				
305					310					315					320				
His	Arg	Gln	Leu	Phe	Ser	Gln	Asp	Trp	Ala	Asp	Ser	Thr	Phe	Ser	Val				
			325					330						335					
Val	Gln	Gln	Gln	Asn	Ser	Asn	Glu	Gln	Lys	Leu	Ile	Ser	Glu	Glu	Asp				
			340					345					350						
Leu	Gly	Gly	Glu	Gln	Lys	Leu	Ile	Ser	Glu	Glu	Asp	Leu	His	His	His				
	355						360					365							
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cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa cacaaactat 180
acacagaatc tccagggcag agtcaccatg accacagaca ctccacgac cacagcctac 240
atggagctga ggagcctgag atctgacgac acggcctgtg attactgtgc gagatggggt 300
atagcaactc gtcctacta ctaactacggg atggacgtct ggggcccaagg gaccacggtc 360
accgtctcct ca                                     372

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Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr				
	20						25					30							
Gly	Ile	Ile	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met				
	35					40					45								
Gly	Trp	Ile	Ser	Gly	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Thr	Gln	Asn	Leu				
	50				55			60											
Gln	Gly	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Thr	Thr	Ala	Tyr				
65				70				75					80						
Met	Glu	Leu	Arg	Ser	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys				
	85						90						95						
Ala	Arg	Trp	Gly	Ile	Ala	Thr	Arg	Pro	Tyr	Tyr	Tyr	Tyr	Gly	Met	Asp				
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Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser								
	115						120												

<210> 382

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<400> 382

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<210> 383

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<212> PRT

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<400> 383

Gly Tyr Thr Phe Thr Ser Tyr Gly
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<210> 384

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<400> 384

atcagcgggt acaatggtaa caca 24

<210> 385

<211> 8

<212> PRT

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Ile Ser Gly Tyr Asn Gly Asn Thr
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<210> 386

<211> 51

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gcgagatggg gtagcaac tcgtccctac tactactacg gtagggacgt c 51

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<400> 387

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1				5					10					15	
Val															

<210> 388

<211> 321

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<400> 388

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gggaaagccc	ctaagtcct	gatctatgct	gcattcagtt	tgcaaagtgg	ggccccatca	180
aagttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ctgccaacag	tataatagtt	accctcccac	tttcggccct	300
gggaccaaaag	tgatatcaaa	a				321

<210> 389

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 389

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Thr	Asn	Tyr
		20						25					30		
Leu	Ala	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Ser	Leu	Ile
		35					40					45			
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Lys	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ser	Tyr	Pro	Pro
				85					90					95	
Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys					
			100						105						

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<400> 390

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<210> 391

<211> 6

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<400> 391

Gln Asp Ile Thr Asn Tyr
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<210> 392

<211> 9

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<223> synthetic

<400> 392

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<210> 393

<211> 3

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<400> 393

Ala Ala Ser
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<210> 394

<211> 27

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<400> 394

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<210> 395

<211> 9

<212> PRT

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<400> 395

Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
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<210> 396

<211> 369

<212> DNA

<213> Artificial Sequence

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<400> 396

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ccagggaagg ggctggagtg ggtctcaact attagtggta gtggtaccag cacatattac 180
gcagactccg tgaagggccg gttcaccatc tccagggaaca attccaggga caccggtgttt 240
ctacaaatga acagcctgag agccgaggac acggccgtat attactgttc gaaaccttct 300
gcattacgat ttttacattg gttatgtatg gacgtctggg gcccaaggga cctggtcacc 360
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<210> 397

<211> 123

<212> PRT

<213> Artificial Sequence

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<400> 397

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20 25 30
Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Thr Ile Ser Gly Ser Gly Thr Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Arg	Asp	Thr	Val	Phe
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90					95		
Ser	Lys	Pro	Ser	Ala	Leu	Arg	Phe	Leu	His	Trp	Leu	Cys	Met	Asp	Val
			100					105					110		
Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser					
		115					120								

<210> 398

<211> 24

<212> DNA

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<400> 398

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<210> 399

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<212> PRT

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<400> 399

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<210> 400

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<213> Artificial Sequence

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<223> synthetic

<400> 400

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<211> 8

<212> PRT

<213> Artificial Sequence

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<400> 401

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<210> 402

<211> 48

<212> DNA

<213> Artificial Sequence

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tcgaaacctt ctgcattacg atttttacat tggttatgta tggacgtc 48

<210> 403

<211> 16

<212> PRT

<213> Artificial Sequence

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<400> 403

Ser Lys Pro Ser Ala Leu Arg Phe Leu His Trp Leu Cys Met Asp Val
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<211> 321

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<400> 404

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gggaaagccc ctaagtcacc gatctatgct gcattccaatt tgcaaagtgg ggtcccatca 180
aggttcggcg gcagtggatc tgggacagat ttcactctca ccatcaacag cctgcagcct 240
gaagattttg taacttatta ctgccagcag tataattctt accctcccac ttctggcgga 300
gggaccaagg tggagatcaa a 321

<210> 405

<211> 107

<212> PRT

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<400> 405

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		20						25					30		
Leu	Asp	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Ser	Leu	Ile
	35						40					45			
Tyr	Ala	Ala	Ser	Asn	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Gly	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Asn	Ser	Leu	Gln	Pro
	65				70					75				80	
Glu	Asp	Phe	Val	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ser	Tyr	Pro	Pro
			85						90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
		100						105							

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<211> 18

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<400> 406

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<210> 407

<211> 6

<212> PRT

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<400> 407

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<210> 408

<211> 9

<212> DNA

<213> Artificial Sequence

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<223> synthetic

<400> 408

gctgcatcc 9

<210> 409

<211> 3

<212> PRT

<213> Artificial Sequence

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<400> 409

Ala Ala Ser
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<210> 410

<211> 27

<212> DNA

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<210> 411

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 411

Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
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REFERENCES CITED IN THE DESCRIPTION

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PATENTKRAV

1. Isoleret antistof eller antigenbindingsfragment deraf, der specifikt binder til human GFR α 3, hvor antistoffet omfatter de tre tungkæde-CDR'er (HCDR1, HCDR2 og HCDR3) og de tre letkæde-CDR'er (LCDR1, LCDR2 og LCDR3) indeholdt i et
5 HCVR/LCVR-aminosyresekvenspar valgt fra gruppen bestående af SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 381/389 og 397/405.

2. Isoleret antistof eller antigenbindingsfragment ifølge krav 1, der omfatter
10 et HCVR/LCVR-aminosyresekvenspar valgt fra gruppen bestående af SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 381/389 og 397/405.

3. Isoleret antistof eller antigenbindingsfragment ifølge krav 2, der omfatter
15 et HCVR/LCVR aminosyresekvenspar valgt fra gruppen bestående af SEQ ID NO: 50/58, 146/154, 210/218 og 290/298.

4. Isoleret monoklonalt antistof eller antigenbindingsfragment deraf ifølge et hvilket som helst af de foregående krav, der har én eller flere af følgende karakteristika:

20 (i) har et K_D i intervallet fra ca. 10^{-8} M til ca. 10^{-13} M målt ved overfladeplasmonresonans;

(ii) udviser evne til at blokere ca. 50-100 % af bindingen af GFR α 3 til dens ligand, artemin, med en IC₅₀-værdi i intervallet fra ca. 40 pM til ca. 15 nM;

(iii) udviser evne til at blokere ca. 20 % til ca. 100 % af bindingen af GFR α 3 til en
25 fast bærer belagt med en blanding af artemin og RET;

(iv) blokerer eller hæmmer artemin-afhængig aktivering af RET med en IC₅₀ i intervallet fra ca. 200 pM til ca. 50 nM;

(v) hæmmer eller reducerer ét eller flere nociceptive responser hos en *in vivo* model af knoglecancersmerte;

30 (vi) hæmmer eller reducerer artemin-sensitiseret termisk hyperalgesi *in vivo*;

(vii) hæmmer eller reducerer allodyn timer hos en *in vivo* model af osteoarthritis; eller

(viii) ikke krydsreagerer med andre GFR-co-receptorer for RET.

5. Isoleret monoklonalt antistof eller antigenbindingsfragment deraf ifølge et hvilket som helst af de foregående krav, hvor:

- 5 (a) antistoffet er valgt fra gruppen bestående af et kimærisk antistof og et humant antistof, og/eller;
- (b) hvor antistoffet ikke krydsreagerer med human GFR α 1 eller human GFR α 2, og/eller;
- (c) hvor antistoffet er et humant monoklonalt antistof, der omfatter (a) en variabel tungkædere region (HCVR) med en aminosyresekvens valgt fra gruppen bestående
- 10 af SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 381 og 397 og (b) en variabel letkædere region (LCVR) med en aminosyresekvens valgt fra gruppen bestående af SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298,
- 15 314, 330, 346, 362, 389 og 405.

6. Isoleret monoklonalt antistof eller antigenbindingsfragment deraf ifølge et hvilket som helst af de foregående krav, hvor:

- (a) antistoffet udviser evne til at blokere ca. 50-95 % af bindingen af human GFR α 3 til dens ligand, artemin, med en IC₅₀-værdi i intervallet fra ca. 40 pM til ca. 750 pM;
- 20 (b) antistoffet eller antigenbindingsfragmentet deraf blokerer ca. 75-100 % af bindingen af human GFR α 3 til dens ligand, artemin, med en IC₅₀-værdi i intervallet fra ca. 400 pM til ca. 15 nM;
- (c) antistoffet eller antigenbindingsfragmentet deraf blokerer eller hæmmer artemin-afhængig aktivering af human RET med en IC₅₀ i intervallet fra ca. 300 pM til ca. 5
- 25 nM; eller
- (d) antistoffet eller antigenbindingsfragmentet deraf blokerer eller hæmmer artemin-afhængig aktivering af cynomolgus RET med en IC₅₀ i intervallet fra ca. 0,7 nM til ca. 2,5 nM.

- 7.** Isoleret nukleinsyremolekyle, der koder for antistoffet eller
- 30 antigenbindingsfragmentet ifølge et hvilket som helst af kravene 1-6.

8. Ekspressionsvektor, der omfatter nukleinsyremolekylet ifølge krav 7.

9. Fremgangsmåde til fremstilling af et anti-GFR α 3-antistof eller antigenbindingsfragment deraf, hvilken Fremgangsmåde omfatter trinnene med indføring af ekspressionsvektoren ifølge krav 8 i en isoleret værtscelle, dyrkning af cellen under forhold, der muliggør fremstilling af antistoffet eller fragmentet deraf, og genvinding af det således fremstillede antistof.

10. Farmaceutisk sammensætning, der omfatter antistoffet eller antigenbindingsfragmentet deraf ifølge et hvilket som helst af kravene 1-6 og en farmaceutisk acceptabel bærer eller fortynder.

11. Farmaceutisk sammensætning, der omfatter et antistof eller antigenbindingsfragment deraf ifølge et hvilket som helst af kravene 1-6 og et andet terapeutisk middel valgt fra gruppen bestående af et opioid, en COX-2-hæmmer, et lokalanæstetikum, en NMDA-modulator, en cannabinoid receptoragonist, en modulator af P2X-familien, en VR1-antagonist, en stof P-antagonist, en anden GFR α 3-antagonist, en cytokin- eller cytokinreceptorantagonist, en nervevækstfaktor- (NGF) hæmmer (en lille molekylær hæmmer eller et anti-NGF-antistof), en hæmmer af BDNF, TrkA, TrkB eller p75, aspirin, et NSAID, et steroid, morfin, en selektiv serotoningenoptagelseshæmmer (SSRI), en serotonin-norepinephrin-genoptagelseshæmmer (SNRI), et tricyklisk stof, en hæmmer af en spændingsafhængig natriumkanal (Nav), en calciumkanalhæmmer, en kaliumkanalhæmmer, en tumornekrosefaktor (TNF) eller TNF-receptorhæmmer, en hæmmer af TWEAK (TNF-relateret WEAK-inducer af apoptose), en RET-hæmmer, en hæmmer af en ligand af GDNF-familien, en hæmmer af GFR α 1, GFR α 2 eller GFR α 4, en hæmmer af en syreregistrerende ionkanal (ASIC1 eller ASIC3), et antikonvulsivum (gabapentin eller pregabalin), en hæmmer af en prekineticinreceptor (PROK1 og PROK2), en caspase-hæmmer, en p38-hæmmer, en IKK1/2-hæmmer, CTLA-4Ig og et kortikosteroid og en farmaceutisk acceptabel bærer eller fortynder;

eventuelt hvor den anden GFR α 3-antagonist er et lille organisk molekyle, en polypeptidantagonist, et andet antistof, der er specifikt for GFR α 3, et siRNA eller et antisensemolekyle, der er specifikt for GFR α 3; eller hvor cytokin- eller

cytokinreceptorantagonisten er en interleukin-1 (IL-1)-antagonist, en IL-6-antagonist eller en IL-18-antagonist.

- 12.** Isoleret antistof eller antigenbindingsfragment deraf ifølge et hvilket som helst af kravene 1-6, eller farmaceutisk sammensætning ifølge enten krav 10 eller
- 5 11, til anvendelse i behandling af en GFR α 3-relateret tilstand eller sygdom, eller smerten forbundet med den GFR α 3-relaterede tilstand eller sygdom, hvor den GFR α 3-relaterede tilstand eller sygdom forebygges, bedres eller reduceres i sværhedsgrad eller hyppighed, eller smerten forbundet med tilstanden eller sygdommen forebygges, bedres eller reduceres i sværhedsgrad eller hyppighed;
- 10 hvor den GFR α 3-relaterede tilstand eller sygdom er valgt fra gruppen bestående af akut smerte, kronisk smerte, neuropatisk smerte, inflammatorisk smerte, et funktionelt smertesyndrom, arthritis, pancreatitis, osteoarthritis, ledsmerter, klyngehovedpine, trigeminal neuralgi, herpetisk neuralgi, generelle neuralgier, neurodegenerative forstyrrelser, bevægelsesforstyrrelser, neuroendokrine
- 15 forstyrrelser, ataksi, visceral smerte, gigt, post-herpetisk neuralgi, diabetisk neuropati, iskias, rygsmerter, hoved- eller halssmerter, svær smerte, eller smerte, der er vanskelig at behandle, gennembrydende smerte, postkirurgisk smerte, arvelig erythromelalgi, dental smerte, rhinitis, cancersmerter, komplekst regionalt smertesyndrom (CRPS), inflammatorisk tarmsygdom (f.eks. Crohns sygdom eller
- 20 ulcerøs colitis) og blæreforstyrrelser.

- 13.** Isoleret antistof, antigenbindingsfragment deraf eller farmaceutisk sammensætning til anvendelse ifølge krav 12, hvor det funktionelle smertesyndrom er valgt fra gruppen bestående af kronisk lændesmerter, irritabel tarmsyndrom (IBS), fibromyalgi (FM), kronisk træthedssyndrom, abdominal smerte, temporomandibulær
- 25 ledforstyrrelse (TMJD), smertefuldt blæresyndrom (interstitiel cystitis), funktionelle gastrointestinale forstyrrelser/syndromer, funktionelt brystsmertesyndrom, migræne og hovedpine af spændingstypen, kronisk bækkensmertesyndrom, smertefuld prostatasyndrom (kronisk prostatitis), multipelt kemisk sensitivitetssyndrom og Golfkrigssyndrom; eller hvor cancersmerten er forbundet med en cancer valgt fra
- 30 gruppen bestående af endometriecancer, prostatacancer, brystcancer, cervixcancer, levercancer, pankreascancer, coloncancer, mavecancer,

uteruscancer, ovariecancer, nyrecancer, ikke-småcellet lungecancer, hjerne­cancer, en leukæmi, et lymfom, knoglecancer og smerte forbundet med cancermetastase.

5 **14.** Antistof, antigenbindingsfragment eller farmaceutisk sammensætning til anvendelse ifølge krav 12 eller 13, hvor antistoffet, antigenbindingsfragmentet eller den farmaceutiske sammensætning er til administration til en patient i kombination med et andet terapeutisk middel; hvor det andet terapeutiske middel eventuelt er som defineret i krav 11.

10 **15.** Isoleret antistof eller antigenbindingsfragment ifølge krav 1, der omfatter en HCDR1-aminosyresekvens ifølge SEQ ID NO: 148; en HCDR2-aminosyresekvens ifølge SEQ ID NO: 150; en HCDR3-aminosyresekvens ifølge SEQ ID NO: 152; en LCDR1-aminosyresekvens ifølge SEQ ID NO: 156; en LCDR2-aminosyresekvens ifølge SEQ ID NO: 158 og en LCDR3-aminosyresekvens ifølge SEQ ID NO: 160.

DRAWINGS

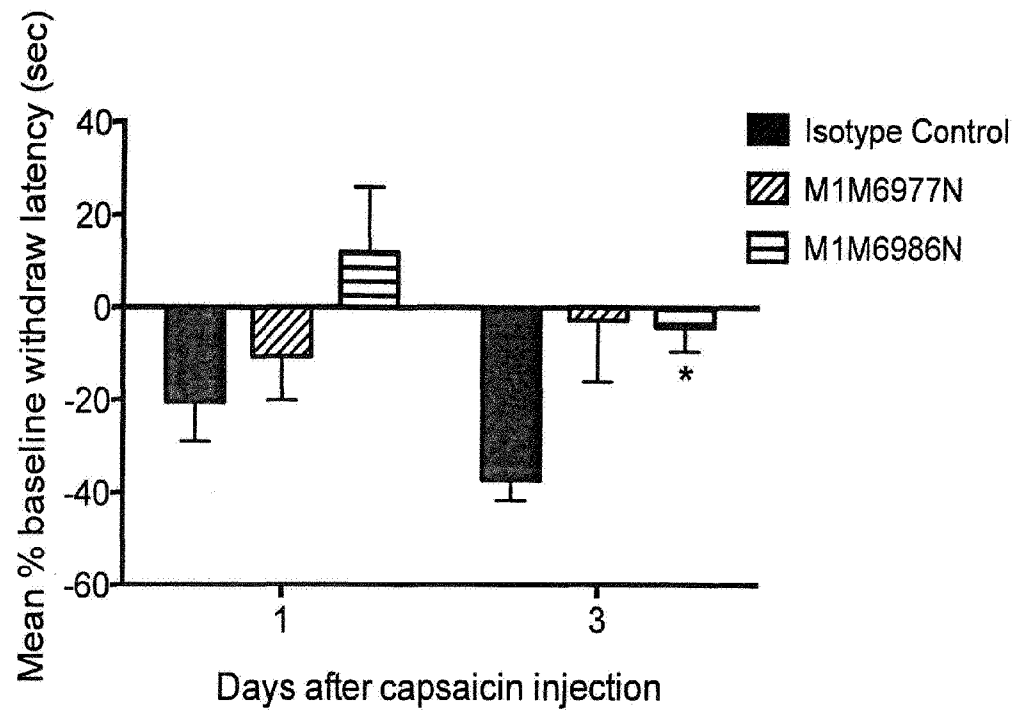


Figure 1

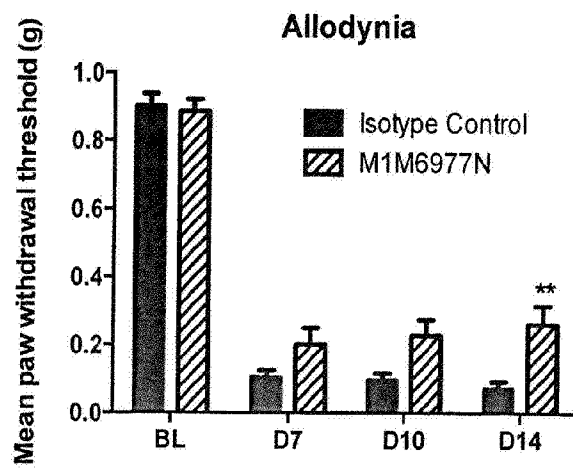
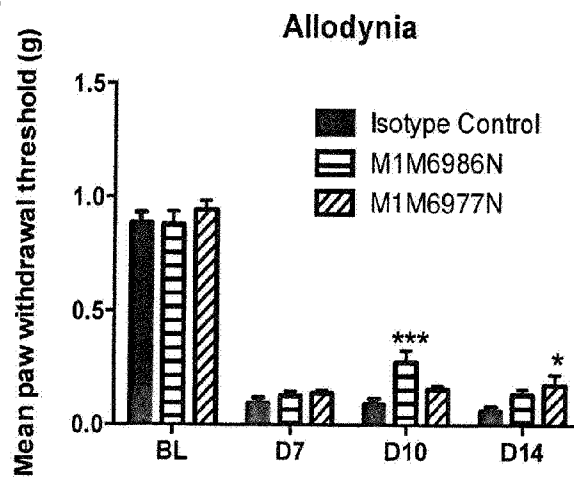
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Figure 2

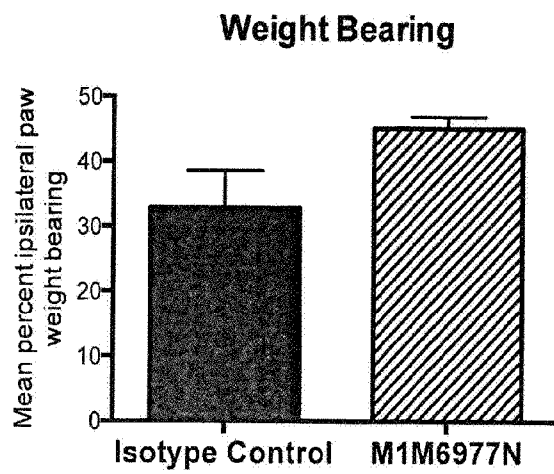
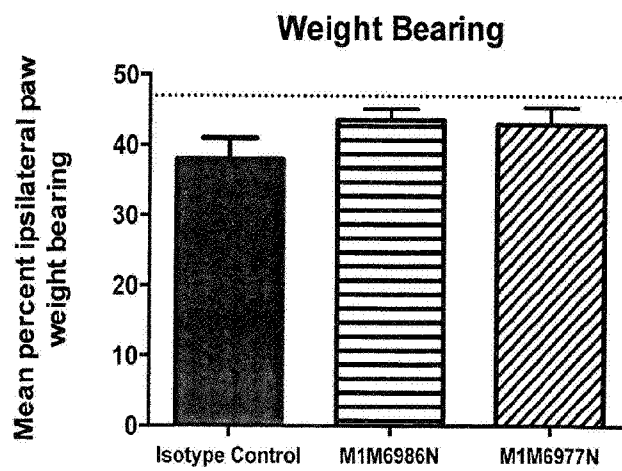
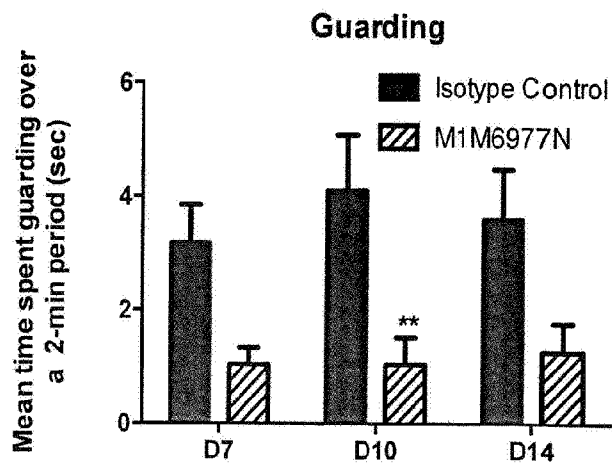
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Figure 3

A.



B.

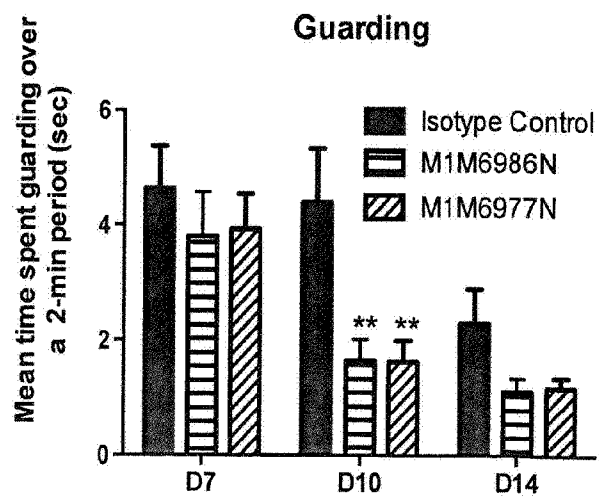


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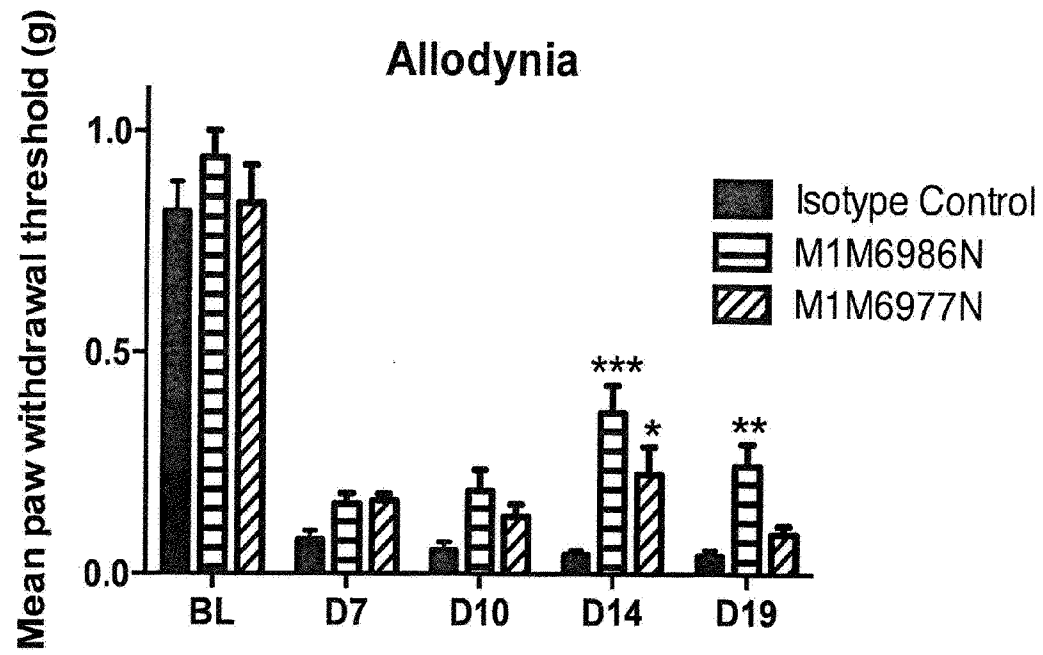


Figure 5

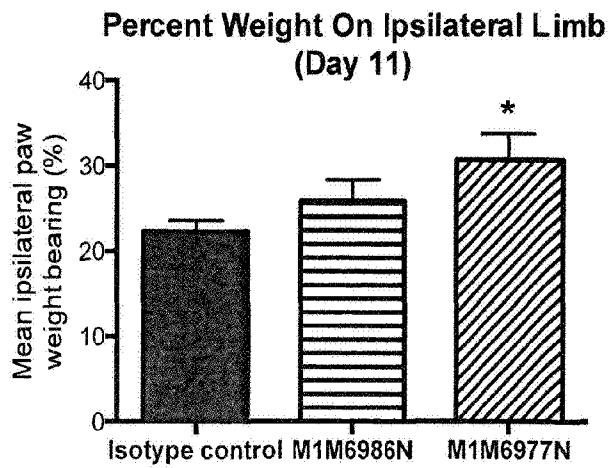
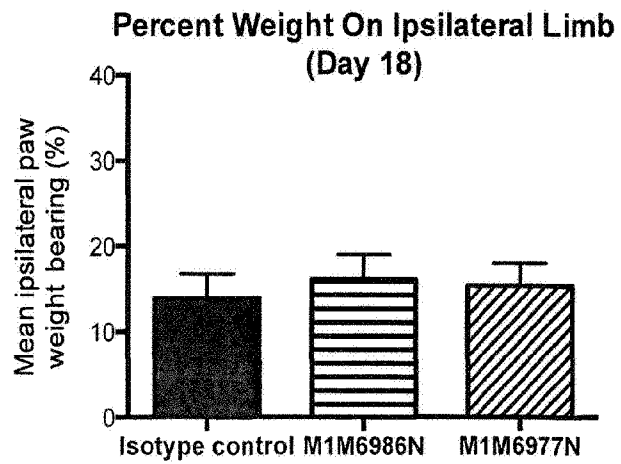
A.**B.**

Figure 6

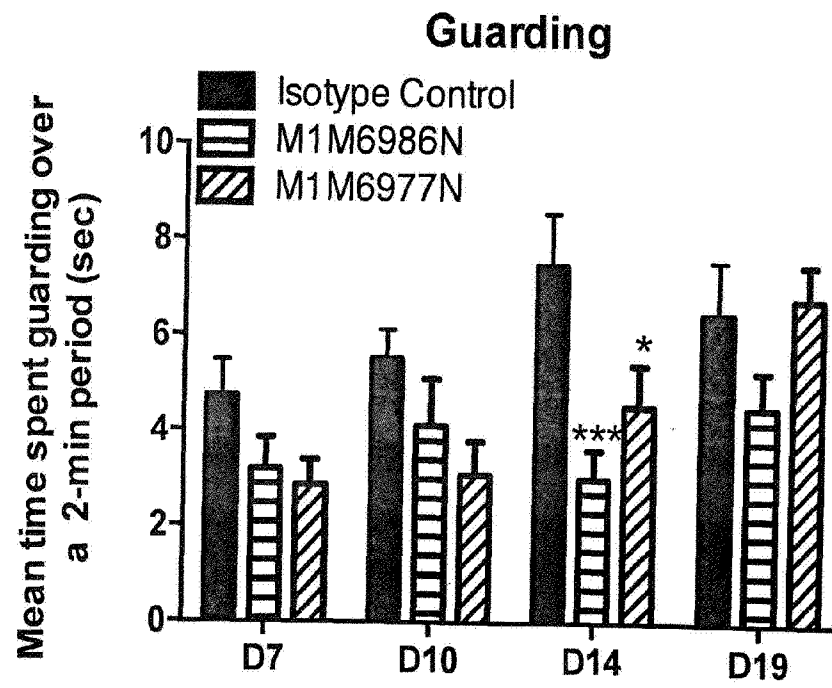


Figure 7

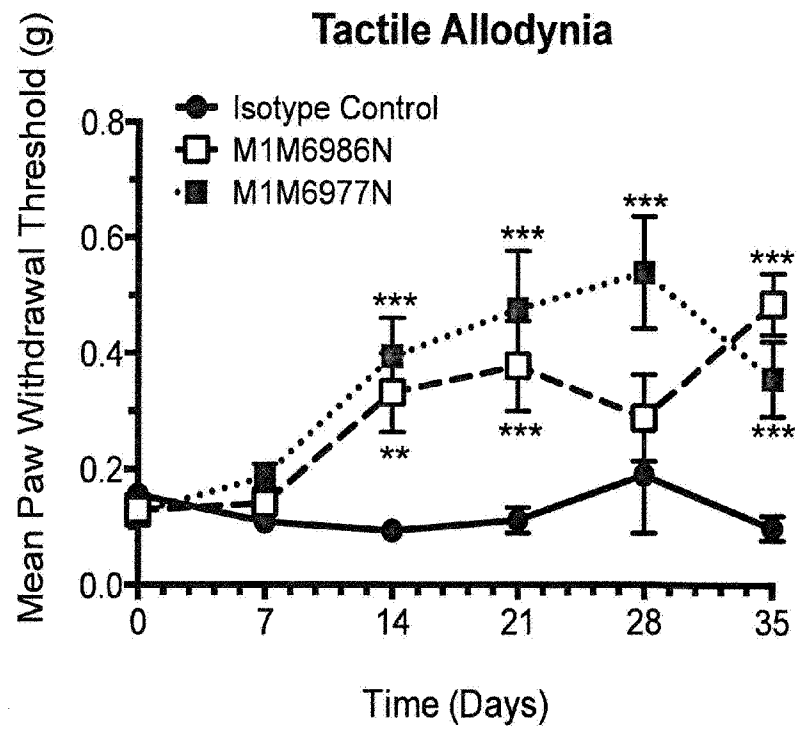


Figure 8

Figure 9

Antibody	Biotin-human GFR α 3 captured (nm)	Amount of Antibody 1 bound (nm)	H4H2236N3	H4H2342P	H4H2295S	H4H2294S	H4H2291S	H4H2357S	H4H2355S	H4H2296S	H4H2243N2	H4H2212N	H4H2352S	H4H2292S	H4H2350P
H4H2236N3	1.07 $\pm$ 0.08	2.64 $\pm$ 0.18	0.00	-0.01	0.03	0.00	0.06	0.04	0.00	0.02	0.02	1.79	1.91	1.81	1.35
H4H2342P	1.09 $\pm$ 0.08	2.69 $\pm$ 0.17	0.20	0.06	0.31	0.23	0.45	0.25	0.16	0.28	0.11	1.76	1.72	1.85	1.46
H4H2295S	1.14 $\pm$ 0.15	2.83 $\pm$ 0.27	0.01	0.01	0.05	0.02	0.20	0.05	0.02	0.07	0.01	1.81	1.85	1.80	1.35
H4H2294S	1.22 $\pm$ 0.04	2.91 $\pm$ 0.09	0.05	0.01	0.04	0.02	0.12	0.03	0.00	0.04	0.03	1.92	1.99	1.92	1.42
H4H2291S	1.16 $\pm$ 0.04	2.89 $\pm$ 0.08	0.01	-0.01	0.00	0.00	0.05	0.00	0.00	-0.01	0.00	1.96	2.03	1.94	1.44
H4H2357S	1.15 $\pm$ 0.03	2.82 $\pm$ 0.07	0.04	-0.01	0.12	0.05	0.18	0.04	0.00	0.06	0.01	1.90	2.00	1.92	1.35
H4H2355S	1.15 $\pm$ 0.03	2.73 $\pm$ 0.07	0.18	0.06	0.20	0.16	0.31	0.16	0.07	0.18	0.09	1.95	1.97	1.92	1.44
H4H2296S	1.29 $\pm$ 0.13	2.88 $\pm$ 0.23	0.07	0.03	0.05	0.04	0.18	0.06	0.02	0.07	0.06	1.76	2.01	1.87	1.27
H4H2243N2	1.10 $\pm$ 0.08	2.42 $\pm$ 0.17	0.30	0.15	0.39	0.29	0.52	0.32	0.24	0.33	0.06	0.22	0.46	1.70	1.20
H4H2212N	1.09 $\pm$ 0.08	2.32 $\pm$ 0.15	2.14	2.17	2.15	2.12	2.89	2.38	2.05	2.36	0.16	0.05	0.08	1.76	1.36
H4H2352S	1.15 $\pm$ 0.03	2.74 $\pm$ 0.16	2.15	2.08	2.31	2.25	2.63	2.45	2.12	2.35	0.13	0.05	0.10	0.15	1.43
H4H2292S	1.17 $\pm$ 0.04	2.82 $\pm$ 0.08	2.24	2.16	2.31	2.31	2.81	2.43	2.07	2.36	1.91	1.78	0.34	0.11	1.53
H4H2350P	1.09 $\pm$ 0.07	3.31 $\pm$ 0.15	1.98	1.80	2.05	2.00	2.57	2.23	1.77	2.10	1.72	1.57	2.06	1.74	0.25