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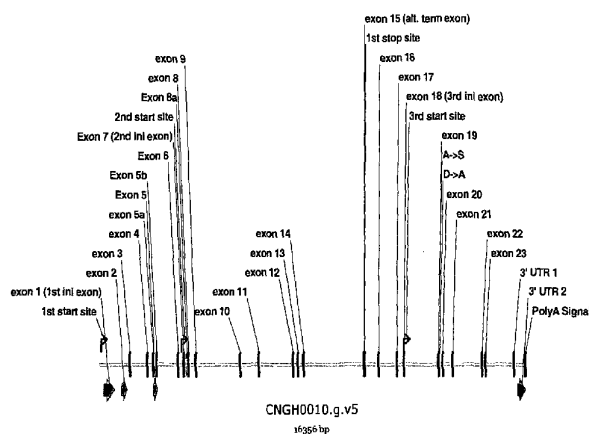
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(54) Title: CNGH0010 SPECIFIC POLYNUCLEOTIDES, POLYPEPTIDES, ANTIBODIES, COMPOSITIONS, METHODS AND USES.



(57) Abstract: Novel polypeptides (CNGH0010) and antibodies, including specified portions or variants, specific for at least one such CNGH0010 polypeptide, variant, or fragment thereof, as well as nucleic acids encoding such CNGH0010 polypeptides and antibodies, complementary nucleic acids, vectors, host cells, and methods of making and using thereof, are useful for therapeutic and diagnostic formulations, administration and devices. The aforesaid polypeptides can be used to generate human, primate, rodent, mammalian, chimeric, humanized and/or CDR-grafted anti-CNGH0010 antibodies. The CNGH0010 polypeptides and antibodies are used in modulating or treating at least one CNGH0010-related disease in a cell, tissue, organ, animal, or patient. Such diseases may include, but are not limited to, psoriasis, rheumatoid arthritis, emphysema, asthma, diabetes, autoimmune thyroiditis, inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, different types of dermatitis including allergic dermatitis, contact dermatitis, actinic keratosis, wound healing, scar formation, various renal diseases, various respiratory diseases, various diseases of reproductive organs, such as endometriosis, melanoma, squamous cell carcinoma, ovarian cancer, breast cancer, lung cancer, colon cancer, prostate cancer, renal cell carcinoma, Grave's diseases and other inflammatory and hyperproliferative diseases.



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**CNGH0010 SPECIFIC POLYNUCLEOTIDES, POLYPEPTIDES,
ANTIBODIES, COMPOSITIONS, METHODS AND USES**

BACKGROUND OF THE INVENTION

5 **A. Field of the Invention**

The present invention relates to CNGH0010 polypeptides, variants, and fragments thereof, and antibodies and anti-idiotypic antibodies specific therefor, as well as nucleic acids encoding such CNGH0010 polypeptides, variants, fragments, antibodies, complementary nucleic acids, vectors, host cells, and methods of making and using
10 thereof, including diagnostic and therapeutic formulations, administration and devices.

B. Background and Related Art

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

15 Psoriasis is a genetic, multifactorial, chronic inflammatory skin disease, with a prevalence of 2.6% in the U.S. population. The disease is characterized by pronounced hyperproliferation of keratinocytes, which results in rapid epidermal turnover and thickened, scaly, red plaques observed clinically. Other prominent histopathological features of the disease are alterations of cytokine production, fibroblast activation,
20 vascular expansion, and leukocyte infiltration in the dermis and epidermis.

Dysregulation in cytokine production from both activated cells in the dermis and the immune cells seems to play an important role in mediating the inflammatory events associated with psoriasis. To this end, a number of changes in gene and/or protein expression have been described previously in psoriasis and some of these genes and/or
25 proteins have also been found to be associated with other inflammatory diseases. These include proinflammatory cytokines such as IL-1 and TNF α , adhesion molecules, such as intercellular adhesion molecule 1 (ICAM1) and vascular adhesion molecule 1 (VCAM1), chemokines, and defensins. Recently, gene expression microarray technology has been applied to profile gene expression patterns in normal versus

psoriatic lesional skins on a more inclusive scale and has provided new insights into the pathogenesis of psoriasis.

- cDNA microarray technology provides a format for the simultaneous measurement of the expression level of thousands of genes in a single hybridization assay. It is also
5 amenable to an automated, high-throughput format. More importantly, microarray technology can be used to discover new genes, quantify and analyze gene expression and assign functionality to genes with unknown function. With the complete sequencing of the human genome, identification and cloning of new genes is now accomplished rapidly. However, the understanding of whether these genes encode new proteins and
10 the further identification of the function of these new proteins have not advanced as rapidly. The impediment has become one of the main reasons for the use of high throughput cDNA microarray technology in a well-designed experimental setting to discover novel protein-encoding genes or genes with novel functions that may subsequently become potential therapeutic targets for a variety of human diseases.
- 15 Accordingly, there is a need to provide new polypeptides, polynucleotides, antibodies, or fragments thereof and uses thereof relevant to diseases and conditions, as well as improvements over known polypeptides, polynucleotides, antibodies or fragments thereof.

SUMMARY OF THE INVENTION

- 20 According to a first aspect, the present invention provides an isolated nucleic acid molecule comprising the nucleotide sequence SEQ ID NO: 2, or an exact complement of said nucleotide sequence.

- According to a second aspect, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having the amino
25 acid sequence SEQ ID NO: 3.

According to a third aspect, the present invention provides an isolated nucleic acid molecule encoding a naturally occurring allelic variant of a polypeptide having the amino acid sequence SEQ ID NO: 3.

According to a fourth aspect, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence having at least 90% identity to SEQ ID NO: 2, or an exact complement of said nucleotide sequence.

According to a fifth aspect, the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence having at least 70% identity to SEQ ID NO: 2, or an exact complement of said nucleotide sequence.

According to a sixth aspect, the present invention provides an isolated polypeptide comprising the amino acid sequence SEQ ID NO: 3.

According to a seventh aspect, the present invention provides an isolated polypeptide comprising an amino acid sequence having at least 90% identity to the amino acid sequence SEQ ID NO: 3.

According to an eighth aspect, the present invention provides a fusion polypeptide comprising the polypeptide of the invention operably linked to a heterologous polypeptide.

According to a ninth aspect, the present invention provides an isolated antibody comprising a monoclonal or polyclonal antibody that specifically binds to a polypeptide of the invention.

According to a tenth aspect, the present invention provides an isolated nucleic acid molecule encoding the antibody of the invention.

According to an eleventh aspect, the present invention provides a vector comprising the nucleic acid molecule of the invention.

According to a twelfth aspect, the present invention provides a host cell containing the nucleic acid molecule of the invention.

According to a thirteenth aspect, the present invention provides a method for producing an isolated antibody, comprising translating the nucleic acid molecule of the invention, under conditions *in vitro*, *in vivo* or *in situ*, wherein the antibody is expressed in detectable or recoverable amounts.

According to a fourteenth aspect, the present invention provides an isolated antibody produced by the method of the thirteenth aspect.

According to a fifteenth aspect, the present invention provides a method for producing an isolated polypeptide, comprising translating the nucleic acid molecule of the
5 invention, under conditions *in vitro*, *in vivo* or *in situ*, wherein the polypeptide is expressed in detectable or recoverable amounts.

According to a sixteenth aspect, the present invention provides an isolated polypeptide produced by the method the fifteenth aspect.

According to a seventeenth aspect, the present invention provides a composition
10 comprising one or more of:

- a) the nucleic acid molecule of the invention,
- b) the polypeptide of the invention, or
- c) the antibody of the invention.

According to an eighteenth aspect, the present invention provides a method of
15 diagnosing a CNGH0010-related condition in a subject, comprising detecting one or more of:

- a) the nucleic acid molecule of the invention,
- b) the polypeptide of the invention, or
- c) the antibody of the invention.

20 According to a nineteenth aspect, the present invention provides a method of treating a CNGH0010-related condition in a subject, comprising administering to the subject the composition of the invention.

According to a twentieth aspect, the present invention provides use of the composition of the invention for the preparation of a medicament for treating a CNGH0010-related
25 condition.

According to a twenty-first aspect, the present invention provides a method of treating an epithelial-related condition in a subject, comprising administering to the subject the composition of the invention.

According to a twenty-second aspect, the present invention provides use the composition of the invention for the preparation of a medicament for treating an epithelial-related condition.

According to a twenty-third aspect, the present invention provides an article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising one or more of:

- a) the nucleic acid molecule of the invention,
- b) the polypeptide of the invention, or
- c) the antibody of the invention.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

The present invention relates to an isolated CNGH0010 polypeptide having the sequence shown in one of SEQ ID NOS: 3, 5, 7, 9, and 11, variants, for example, those based on differential exon splicing as described in Table 2 below, and fragments thereof. Another aspect of the invention is an isolated polynucleotide comprising the sequence shown in one of SEQ ID NOS:2, 4, 6, 8, and 10, variants (e.g., those based on differential exon splicing as described in Table 2 below) and fragments thereof, and complementary sequences. Another aspect of the invention is an isolated polynucleotide comprising a polynucleotide encoding the amino acid sequence shown in one of SEQ ID NOS:3, 5, 7, 9, and 11, variants (e.g., those based on differential exon splicing as described in Table 2 below) and fragments thereof, and complementary sequences.

The invention also relates to isolated polypeptides having at least 70%, preferably, 75%, 80%, 90%, 95%, 99%, or 100% amino acid sequence identity to any of the amino acid sequences of SEQ ID NOS:3, 5, 7, 9, and 11, variants, or fragments thereof; isolated polynucleotides having at least 70%, preferably, 75%, 80%, 90%, 95%, 99%, or 100% nucleic acid sequence identity to any of the polynucleotide sequences of SEQ ID NOS:2, 4, 6, 8, and 10, variants, complementary sequences, or fragments thereof; and isolated polynucleotides having at least 70%, preferably, 75%, 80%, 90%, 95%, 99%, or 100% nucleic acid sequence identity to the polynucleotides encoding any of the amino acid

sequences of SEQ ID NOS:3, 5, 7, 9, and 11 and variants, complementary sequences, or fragments thereof.

The present invention also provides isolated nucleic acid molecules hybridizing to (a) a nucleic acid molecule encoding a polypeptide which has at least 70% amino acid
5 sequence identity to an amino acid sequence of one of SEQ ID NOS:3, 5, 7, 9, and 11, variants, and fragments thereof, or (b) a nucleic acid molecule having at least 70% sequence identity to any of the polynucleotide sequences of SEQ ID NOS:2, 4, 6, 8, and 10, variants, and fragments thereof, and complementary nucleic acids. The present invention further provides recombinant vectors comprising the polypeptide encoding
10 nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such nucleic acids, vectors and/or host cells.

In another aspect, the present invention relates to antibodies and antibody fragments capable of binding to (a) a polypeptide having at least 70% amino acid sequence identity
15 to all or part of an amino acid sequence of one of SEQ ID NOS:3, 5, 7, 9, and 11 or variants, or (b) a polypeptide encoded by a polynucleotide having at least 70% nucleic acid identity to all or part of any of the polynucleotide sequences of SEQ ID NOS:2, 4, 6, 8, and 10 or variants. In addition, the invention comprises antibody compositions, formulations, devices, and transgenic mice and plants. The present invention also
20 provides methods for generating and characterizing human, primate, rodent, mammalian, chimeric, single chain, humanized and/or CDR-grafted anti-CNGH0010 antibodies, immunoglobulins, cleavage products and other specified portions and variants thereof. The present invention further provides at least one CNGH0010 anti-idiotypic antibody to at least one CNGH0010 antibody of the present invention.

polynucleotide sequences of SEQ ID NOS:2, 4, 6, 8, and 10 or variants. In addition, the invention comprises antibody compositions, formulations, devices, and transgenic mice and plants. The present invention also provides methods for generating and characterizing human, primate, rodent, mammalian, chimeric, single chain, humanized and/or CDR-grafted anti-CNGH0010 antibodies, immunoglobulins, cleavage products and other specified portions and variants thereof. The present invention further provides at least one CNGH0010 anti-idiotypic antibody to at least one CNGH0010 antibody of the present invention.

The nucleic acid sequences encoding CNGH0010 polypeptides, or fragments thereof, can be operably linked to a nucleic acid sequence encoding a heterologous amino acid sequence to form a fusion protein. A further embodiment is a mimetibody which comprises at least a fragment of a CNGH0010 polypeptide fused to at least part of an immunoglobulin region. A preferred mimetibody comprises at least one CH₃ region directly linked with at least one CH₂ region directly linked with at least one hinge region or fragment thereof optionally directly linked with at least one partial V region, directly linked with an optional linker sequence, directly linked to at least a fragment of a CNGH0010 polypeptide, optionally, further directly linked with at least a portion of at least one variable antibody sequence. In a further preferred embodiment, the immunoglobulin is IgG1 or IgG4.

Another aspect of the invention provides recombinant expression vectors, comprising a CNGH0010 polynucleotide. In another embodiment, the invention provides isolated host cells, e.g., mammalian and non-mammalian cells, containing such a vector and/or a CNGH0010 polynucleotide. The invention also provides methods for producing a CNGH0010 polypeptide by culturing, in a suitable medium, a host cell of the invention containing a recombinant expression vector encoding a CNGH0010 polypeptide such that the polypeptide is produced.

The present invention also provides at least one method for expressing a CNGH0010 polypeptide, anti-CNGH0010 antibody, or CNGH0010 anti-idiotypic antibody, in a host cell, comprising culturing a host cell as described herein under conditions wherein at least one such CNGH0010 polypeptide, anti-CNGH0010 antibody or CNGH0010 anti-idiotypic antibody is expressed in detectable and/or recoverable amounts.

In yet another aspect, the present invention provides a fusion protein comprising a polypeptide which has at least 70%, preferably, 75%, 80%, 90%, 95%, 99%, or 100% amino acid sequence identity to an amino acid sequence of one of SEQ ID NOS:3, 5, 7, 9, and 11, fused to a heterologous amino acid sequence.

The present invention also provides at least one composition comprising (a) an isolated CNGH0010 polynucleotide, polypeptide, polypeptide agonist or antagonist, antibody, and/or anti-idiotypic antibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, according to known carriers or diluents. The composition can optionally further comprise at least one further compound, protein or composition.

The present invention also relates to methods of treatment and/or diagnosis of CNGH0010 related diseases, such as but not limited to, psoriasis, rheumatoid arthritis, emphysema, asthma, diabetes, autoimmune thyroiditis, inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, different types of dermatitis including allergic dermatitis, contact dermatitis, actinic

5 keratosis, wound healing, scar formation, various renal diseases, various respiratory diseases, various diseases of reproductive organs, such as endometriosis, melanoma, squamous cell carcinoma, ovarian cancer, breast cancer, lung cancer, colon cancer, prostate cancer, renal cell carcinoma, Grave's diseases and other inflammatory and hyperproliferative diseases. In a preferred embodiment, the CNGH0010 related disease is an epithelial-related disease or condition such that the disease or

10 condition impacts epithelial cells and related cells, including, without limitation, psoriasis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, different types of dermatitis (allergic dermatitis, contact dermatitis), Actinic keratosis, wound healing, scar formation, different renal diseases, different respiratory diseases, different diseases of reproductive organs such as endometriosis, melanoma, squamous cell carcinoma, ovarian cancer, breast cancer, lung cancer,

15 colon cancer, prostate cancer, renal cell carcinoma, emphysema, Grave's disease, diabetes, pemphigus, bullous pemphigoid, Herpes, Linear IgA disease, drug eruption, epidermolysis bullosa, stomatitis, aphthous ulcer, peptic ulcers, gastric polyposis, chronic obstructive pulmonary diseases, bronchiectasis, cystic fibrosis, renal cystic disease, cystitis, and other inflammatory and hyperproliferative diseases. The methods utilize (1) an isolated polypeptide comprising at least one of

20 the sequences selected from SEQ ID NOS:3, 5, 7, 9, and 11, variants, derivatives, and fragments thereof, (2) an isolated polynucleotide comprising at least one of the sequences of SEQ ID NOS:2, 4, 6, 8, and 10, variants, derivatives, and fragments thereof, and complementary sequences, (3) an isolated polypeptide encoded by a polynucleotide comprising at least one of the sequences of SEQ ID NOS:2, 4, 6, 8, and 10, variants and fragments thereof, and (4) agonists and antagonists to such

25 polypeptides and nucleotide to diagnose and/or treat inflammatory and hyperproliferative diseases and conditions. The present invention also provides methods of treatment and/or diagnosis of CNGH0010 related diseases utilizing a CNGH0010 agonist or antagonist, anti-CNGH0010 antibody and/or CNGH0010 anti-idiotypic antibody.

The present invention further provides any invention described herein.

30

DESCRIPTION OF THE FIGURES

Figure 1 shows the genomic structure of the CNGH0010 gene with exons being represented by vertical lines and the transcription start sites represented by curved arrows.

Figure 2 shows relative transcript levels as determined by RT-PCR using RNA from A431

35 cells.

Figure 3 shows predicted protein domains based on expression data and analysis of the amino acids coded by CNGH0010 transcripts.

Figure 4 shows SDS-PAGE analysis of CNGH0010.2 expressed in HEK293 cells in reduced and non-reduced samples.

DESCRIPTION OF THE INVENTION

5 As used herein, "CNGH0010 polypeptide(s) or protein(s)," or "polypeptide(s) or protein(s) of the invention" encompass isolated polypeptides comprising at least one of the sequences selected from SEQ ID NOS:3, 5, 7, 9, and 11, variants, derivatives, and fragments thereof. "CNGH0010 nucleic acids, polynucleotide(s), or gene(s)," or "nucleic acids, polynucleotide(s), or gene(s) of the invention" refer to isolated polynucleotides comprising at least one of the sequences of SEQ ID
10 NOS:2, 4, 6, 8, and 10, variants, derivatives, and fragments thereof, and complementary sequences.

Splice variants of the CNGH0010 protein and nucleic acids encoding these variants have been identified in epithelial cell types through use of RACE, RT-PCR, and Northern blot techniques. The exons and untranslated regions of the genomic CNGH0010 DNA sequence (SEQ ID NO:1) were identified (Table 1). As shown in Table 2, the CNGH0010 gene has multiple possible variants as a
15 result of differential transcription initiation and termination sites, i.e., alternative splicing. The primary variants are labeled CNGH0010.1, CNGH0010.2, CNGH0010.3, CNGH0010.4, and CNGH0010.5 (represented by SEQ ID NOS:2, 4, 6, 8, and 10 (nucleic acids) and 3, 5, 7, 9, and 11 (amino acids), respectively). Additional variants of the invention are encompassed by different combinations of exons as seen in analysis of the genomic sequence and RT-PCR products. This is
20 demonstrated in Table 2 as shown by the exons that may be added or deleted to the coding sequences.

RT-PCR analysis of CNGH0010 transcripts present in A431 cells indicate that the CNGH0010.1 transcripts are heterogeneous with regard to the presence or absence of at least exons 11 and 20, whereas the CNGH0010.2 transcripts have heterogeneity with regard to exon 9. Also, CNGH0010.4 transcripts are heterogeneous with regard to the presence or absence of exons 9, 10, 11,
25 and 12.

The similarities of the CNGH0010 molecules to extracellular matrix molecules (collagens) and cytokines (adiponectin) suggest that they may participate in the regulation of cell-cell or cell-matrix interactions, or bind to or influence the binding of a cytokine to a receptor. Both types of activities would ultimately influence the proliferation, migration, and differentiation status of cells
30 and tissues. Therefore, proteins and polynucleotides of the invention represent ideal targets for therapeutic intervention using monoclonal antibodies, synthetic polypeptides, small molecule drugs, or other natural or synthetic drugs.

Accordingly, the present invention provides novel amino acid and nucleic acid sequences identified as the CNGH0010 protein and gene. The sequences comprise an isolated polypeptide comprising a polypeptide having the sequence shown in one of SEQ ID NOS:3, 5, 7, 9, and 11 or
35 variants thereof; an isolated polynucleotide comprising a polynucleotide having the sequence shown in one of SEQ ID NOS:2, 4, 6, 8, and 10 or a complementary sequence; an isolated polynucleotide

comprising a polynucleotide encoding the amino acid sequence shown in one of SEQ ID NOS:3, 5, 7, 9, and 11 or a complementary sequence; isolated polypeptides comprising a polypeptide having at least 70% amino acid sequence identity to any of the amino acid sequences of SEQ ID NOS:3, 5, 7, 9, and 11 or variants thereof; isolated polynucleotides having at least 70% nucleic acid sequence identity to any of the polynucleotide sequences of SEQ ID NOS:2, 4, 6, 8, and 10, complementary sequences, or variants thereof; isolated polynucleotides having at least 70% nucleic acid sequence identity to the polynucleotides encoding any of the amino acid sequences of SEQ ID NOS:3, 5, 7, 9, and 11, complementary sequences, or variants thereof; and isolated nucleic acid molecules hybridizing to a nucleic acid molecule encoding a polypeptide which has at least 70% amino acid sequence identity to an amino acid sequence of one of SEQ ID NOS:3, 5, 7, 9, and 11, a nucleic acid molecule having at least 70% sequence identity to any of the polynucleotide sequences of SEQ ID NOS:2, 4, 6, 8, and 10, or complementary nucleic acids; and fragments of these polypeptide and polynucleotide sequences.

As used herein, "identity," as known in the art, is a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between polypeptide or polynucleotide sequences, as determined by the match between strings of such sequences. "Identity" and "similarity" can be readily calculated by known methods, including, but not limited to, those described in (Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo, H., and Lipman, D., Siam J. Applied Math., 48:1073 (1988)). In addition, values for percentage identity can be obtained from amino acid and nucleotide sequence alignments generated using the default settings for the AlignX component of Vector NTI Suite 8.0 (Informax, Frederick, MD).

Preferred methods to determine identity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in publicly available computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, the GCG program package (Devereux, J., et al., Nucleic Acids Research 12(1): 387 (1984)), BLASTP, BLASTN, and FASTA (Atschul, S. F. et al., J. Molec. Biol. 215:403-410 (1990)). The BLAST X program is publicly available from NCBI and other sources (BLAST Manual, Altschul, S., et al., NCBI/NIH Bethesda, Md. 20894; Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990)). The well-known Smith Waterman algorithm may also be used to determine identity.

Preferred parameters for polypeptide sequence comparison include the following:

(1) Algorithm: Needleman and Wunsch, J. Mol Biol. 48:443-453 (1970) Comparison matrix:

BLOSSUM62 from Hentikoff and Hentikoff, Proc. Natl. Acad. Sci, USA. 89:10915-10919 (1992)

Gap Penalty: 12

Gap Length Penalty: 4

- 5 A program useful with these parameters is publicly available as the "gap" program from Genetics Computer Group, Madison Wis. The aforementioned parameters are the default parameters for polypeptide comparisons (along with no penalty for end gaps).

Preferred parameters for polynucleotide comparison include the following:

(1) Algorithm: Needleman and Wunsch, J. Mol Biol. 48:443-453 (1970)

Comparison matrix: matches=+10, mismatch=0

10 Gap Penalty: 50

Gap Length Penalty: 3

Available as: The "gap" program from Genetics Computer Group, Madison Wis. These are the default parameters for nucleic acid comparisons.

- By way of example, a polynucleotide sequence of the present invention may be identical to the sequence of SEQ ID NO:2, that is be 100% identical, or it may include up to a certain integer number of nucleotide alterations as compared to the reference sequence. Such alterations are selected from the group consisting of at least one nucleotide deletion, substitution, including transition and transversion, or insertion, and wherein the alterations may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The number of nucleotide alterations is determined by multiplying the total number of nucleotides in SEQ ID NO:2 by the numerical percent of the respective percent identity (divided by 100) and subtracting that product from the total number of nucleotides in SEQ ID NO:2, or:

25
$$n_{\text{sub}.n} - \text{Int}(\frac{n_{\text{sub}.n} \times y}{100})$$

wherein $n_{\text{sub}.n}$ is the number of nucleotide alterations, $x_{\text{sub}.n}$ is the total number of nucleotides in SEQ ID NO:2, and y is, for instance, 0.70 for 70%, 0.80 for 80%, 0.85 for 85%, 0.90 for 90%, 0.95 for 95%, etc., and wherein any non-integer product of $x_{\text{sub}.n}$ and y is rounded down to the nearest integer prior to subtracting from $x_{\text{sub}.n}$.

- Alterations of a polynucleotide sequence encoding the polypeptide of SEQ ID NO:3 may create nonsense, missense or frameshift mutations in this coding sequence and thereby alter the polypeptide encoded by the polynucleotide following such alterations. Similarly, a polypeptide sequence of the present invention may be identical to the reference sequence of SEQ ID NO:3, that is be 100% identical, or it may include up to a certain integer number of amino acid alterations as compared to the reference sequence such that the percentage identity is less than 100%. Such alterations are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitutions, or insertions, and wherein the alterations

may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between those terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. The number of amino acid alterations for a given % identity is determined by multiplying the total number of amino acids in SEQ ID NO:3 by the numerical percent of the respective percent identity (divided by 100) and then subtracting that product from the total number of amino acids in SEQ ID NO:3, or:

$$n_{\text{sub.a}} - (x_{\text{sub.a}} \times y)$$

wherein $n_{\text{sub.a}}$ is the number of amino acid alterations, $x_{\text{sub.a}}$ is the total number of amino acids in SEQ ID NO:3, and y is, for instance, 0.70 for 70%, 0.80 for 80%, 0.85 for 85% etc., and wherein any non-integer produce of $x_{\text{sub.a}}$ and y is rounded down to the nearest integer prior to subtracting it from $x_{\text{sub.a}}$.

As used herein, a "fragment" is a variant polypeptide having an amino acid sequence that is entirely the same as part but not all of any amino acid sequence of any polypeptide of the invention or a variant polynucleotide having a nucleic acid sequence that is entirely the same as part but not all of any nucleic acid sequence of any polynucleotide of the invention. Fragments can include, e.g., truncation polypeptides having a portion of an amino acid sequence as shown in the amino acid sequences of SEQ ID NOS:3, 5, 7, 9, or 11 or of variants thereof, such as a continuous series of residues that include a heterologous amino- and/or carboxy-terminal amino acid sequence. Degradation forms of the polypeptides of the invention produced by or in a host cell are also included. Other exemplary fragments are characterized by structural or functional attributes, such as fragments that comprise alpha-helix or alpha-helix forming regions, beta-sheet or beta-sheet forming regions, turn or turn-forming regions, coil or coil-forming regions, hydrophilic regions, hydrophobic regions, alpha-amphipathic regions, beta-amphipathic regions, flexible regions, surface-forming regions, substrate binding regions, extracellular regions and high antigenic index regions.

Further exemplary fragments include an isolated polypeptide comprising an amino acid sequence having at least 15, 20, 30, 40, 50 or 100 contiguous amino acids from the amino acid sequence set forth in SEQ ID NOS:3, 5, 7, 9, or 11 and variants, or an isolated polypeptide comprising an amino acid sequence having at least 15, 20, 30, 40, 50 or 100 contiguous amino acids truncated or deleted from the amino acid sequence set forth in amino acid sequence shown in SEQ ID NOS:3, 5, 7, 9, or 11 and variants. Fragments also include isolated polynucleotides having similar sizes and characteristics.

The polypeptides and derivatives of the invention are useful as agents to inhibit the binding of the CNGH0010 polypeptide to its ligand and reduce or block subsequent signal transduction. The polypeptides and polypeptide constructs can be used as immunogens or as binding partners useful for generating, selecting, and characterizing human, primate, rodent, mammalian, chimeric, single chain, humanized and/or CDR-grafted anti-CNGH0010 antibodies, immunoglobulins, cleavage products and other specified portions and variants thereof. In addition, the antibody amino acid sequences, and

encoding nucleic acid molecules comprising at least one polynucleotide encoding at least one anti-CNGH0010 antibody or anti-idiotypic antibody can be determined by methods well-known in the art and as described herein.

At least one human CNGH0010 polypeptide sequence as described herein is antigenic and offers a method for the generation of anti-CNGH0010 antibodies. The polypeptides described herein comprise a new class of CNGH0010 antigens that contain critical epitopes for diagnostic and therapeutic CNGH0010 antibodies. The polypeptides can be synthesized as described herein based on the amino acid sequence of the human CNGH0010 polypeptide sequences of the invention.

The CNGH0010 polypeptide or anti-CNGH0010 antibody can be incorporated into a method or composition for administering a therapeutically or prophylactically effective amount to modulate or treat at least one CNGH0010-related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein. The CNGH0010 polypeptide or anti-CNGH0010 antibody can be incorporated into a method or composition for diagnosing at least one CNGH0010-related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The CNGH0010 polypeptide or anti-CNGH0010 antibody can be incorporated into a method for diagnosing or treating a CNGH0010-related condition in a cell, tissue, organ or animal, comprising contacting or administering a composition comprising an effective amount of at least one isolated CNGH0010 polypeptide or anti-CNGH0010 antibody composition of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.001-50 mg/kilogram of the polypeptide or antibody. The method can optionally further comprise treating the CNGH0010-related condition with the polypeptide or antibody by administering the polypeptide or antibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

The present invention provides for novel proteins and polypeptides from CNGH0010's receptor binding region that can be used to generate anti-CNGH0010 antibodies and fragments thereof. First, the methods of identifying, isolating, and creating the novel polypeptides are discussed below. Then, the generation of antibodies, applications, formulations, and therapeutic treatments are presented.

All publications cited herein are entirely incorporated herein by reference, whether or not specifically designated accordingly, as they show the state of the art at the time of the present

invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats. The following references are entirely incorporated herein by reference: Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001).

10 A human CNGH0010 polypeptide of the present invention includes those of SEQ ID NOS:3, 5, 7, 9, and 11 and their variants, including, without limitation, alternative splice variants, and can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein. Such mutations or substitutions can include muteins, whose mutations can be significant enough to alter the properties of the polypeptide without altering the biological activity of the polypeptide to inhibit the binding of human CNGH0010 to its ligand. 15 Included within the invention are CNGH0010 polypeptides having amino acid sequences in addition to those of SEQ ID NOS:3, 5, 7, 9, and 11 and their variants.

Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid 20 substitutions, insertions or deletions for any given CNGH0010 polypeptide, fragment or variant will not be more than 1-5, or any range or value therein, as specified herein.

Amino acids in a CNGH0010 polypeptide of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, *supra*, Chapters 8, 15; Cunningham and Wells, Science 25 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to, at least one CNGH0010 neutralizing activity.

Synthesis of CNGH0010 polypeptides

30 Polypeptides having the amino acid sequences set forth and described above, may be synthesized using standard Boc or Fmoc chemistry. The resulting polypeptides can be injected as is, cross-linked, or conjugated to a carrier molecule. To facilitate conjugation to carriers, an N-terminal N-acetyl-cysteine or C-terminal amides can be formed and the C-terminal amino acid can be amidated. A variety of linking groups may be interspaced between the polypeptide and the carrier 35 molecule to allow for proper conformational folding and presentation of the antigenic polypeptide.

It is envisioned that the CNGH0010 polypeptides of this invention may also be produced by cell lines derived from bacteria, yeast, insect, or mammal. Recombinant expression cassettes comprising the nucleic acids encoding the novel polypeptides can be introduced into at least one host cell. Vectors containing the CNGH0010 nucleic acid sequence and necessary promoter elements may
5 be used to express CNGH0010 polypeptides. Nucleic acid sequences encoding a CNGH0010 polypeptide in conjunction with a signal peptide may be included to facilitate secretion and purification of desired polypeptides. Those of ordinary skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a polypeptide of the present invention. Cell-free translation systems can also be employed to produce such polypeptides
10 using RNAs derived from the DNA constructs of the invention.

Nucleic Acid Molecules

Nucleic acid sequences encoding human CNGH0010 polypeptides of the present invention may be obtained by cloning, for example, by RT-PCR amplification of RNA samples. Alternatively,
15 the DNA encoding CNGH0010 polypeptides may be obtained by DNA synthesis or from any cDNA library prepared from tissues believed to possess the CNGH0010 mRNA or from a genomic DNA library. The nucleic acid sequences can be cloned by PCR amplification or by traditional methods of DNA hybridization and expression cloning.

Using the information provided herein (methods described herein or as known in the art),
20 such as the nucleotide sequences encoding at least 70-100% of the contiguous amino acids of at least one of SEQ ID NOS:3, 5, 7, 9, and 11 or specified fragments, variants or consensus sequences thereof, or a vector comprising at least one of these sequences, a nucleic acid molecule of the present invention encoding at least one CNGH0010 polypeptide or anti-CNGH0010 antibody can be obtained.

Nucleic acid molecules of the present invention can be in the form of RNA, such as mRNA,
25 hnRNA, or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations thereof. The DNA can be triple-stranded, double-stranded or single-stranded, or any combination thereof. Any portion of at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as the anti-sense strand.

30 As indicated herein, nucleic acid molecules of the present invention which comprise a nucleic acid encoding a CNGH0010 polypeptide or anti-CNGH0010 antibody can include, but are not limited to, those encoding the amino acid sequence of a polypeptide or antibody fragment, by itself; the coding sequence for the entire polypeptide or antibody or a portion thereof; the coding sequence for a polypeptide or antibody, fragment or portion, as well as additional sequences, such as the coding
35 sequence of at least one signal leader or fusion peptide, with or without the aforementioned additional coding sequences, such as at least one intron, together with additional, non-coding sequences, including but not limited to, non-coding 5' and 3' sequences, such as the transcribed, non-translated

sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals (for example, ribosome binding and stability of mRNA); and an additional coding sequence that codes for additional amino acids, such as those that provide additional functionalities. Thus, the sequence encoding a polypeptide or antibody can be fused to a marker sequence, such as a sequence
5 encoding a peptide that facilitates purification of the fused antibody comprising an antibody fragment or portion thereof.

Construction of Nucleic Acids and Expression and Purification of Polypeptides

The isolated nucleic acids of the present invention can be made using (a) recombinant methods, (b) synthetic techniques, (c) purification techniques, or combinations thereof, as well-known
10 in the art.

The nucleic acids can conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide of the present
15 invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the proteins of the present invention. The nucleic acid of the present invention - excluding the coding sequence - is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention.

Additional sequences can be added to such cloning and/or expression sequences to optimize
20 their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

A great variety of expression systems can be used to produce the polypeptides of the invention. Such systems include chromosomal-, episomal- and virus-derived vectors, such as vectors
25 derived from bacterial plasmids, bacteriophage, transposons, yeast episomes, insertion elements, yeast chromosomal elements, baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses, picornaviruses and retroviruses and vectors derived from combinations thereof, such as cosmids and phagemids. The expression system constructs may contain control regions that regulate or cause expression. Generally, any system or vector suitable to maintain
30 or propagate polynucleotides and/or to express polypeptides in a host may be used for expression. An appropriate DNA sequence may be inserted into the expression system by any of a variety of techniques well known to those skilled in the art, such as, e.g., those set forth in Sambrook *et al.*, *supra*.

In eukaryotic expression systems, polypeptides of the invention can be secreted into the
35 lumen of the endoplasmic reticulum or extracellular environment by inclusion of appropriate secretion signals, such as a signal peptide or leader sequence.

Polypeptides of the invention can be recovered and purified from recombinant cell cultures by well-known methods, including ammonium sulfate or ethanol precipitation, acid extraction, high-performance liquid chromatography, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxyapatite chromatography and lectin chromatography. Well-known techniques for refolding protein may be employed to regenerate an active conformation when the protein is denatured during isolation and/or purification.

In an alternate method of obtaining the nucleic acid of the invention, encoding the CNGH0010 polypeptides, a cDNA or genomic library can be screened using a probe based upon the sequence of a polynucleotide of the present invention, such as those disclosed herein. Probes can be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different organisms. Those of skill in the art will appreciate that various degrees of stringency of hybridization can be employed in the assay; and either the hybridization or the wash medium can be stringent. As the conditions for hybridization become more stringent, there must be a greater degree of complementarity between the probe and the target for duplex formation to occur. The degree of stringency can be controlled by one or more of temperature, ionic strength, pH and the presence of a partially denaturing solvent, such as formamide.

For example, the stringency of hybridization is conveniently varied by changing the polarity of the reactant solution through, for example, manipulation of the concentration of formamide within the range of 0% to 50%. The degree of complementarity (sequence identity) required for detectable binding will vary in accordance with the stringency of the hybridization medium and/or wash medium. The degree of complementarity will optimally be 100%, or 80-100%, or any range or value therein. However, it should be understood that minor sequence variations in the probes and primers can be compensated for by reducing the stringency of the hybridization and/or wash medium. An example of stringent hybridization conditions includes overnight incubation at 42°C in a solution comprising: 50% formamide, 5XSSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5XDenhardt's solution, 10% dextran sulfate, and 20 microgram/ml denatured, sheared salmon sperm DNA; followed by washing the filters in 0.1XSSC at about 65°C.

Methods of amplification of RNA or DNA are well known in the art and can be used according to the present invention without undue experimentation, based on the teaching and guidance presented herein. Known methods of DNA or RNA amplification include, but are not limited to, polymerase chain reaction (PCR) and related amplification processes (see, e.g., U.S. Patent Nos. 4,683,195, 4,683,202, 4,800,159, 4,965,188, to Mullis, et al.; 4,795,699 and 4,921,794 to Tabor, et al; 5,142,033 to Innis; 5,122,464 to Wilson, et al.; 5,091,310 to Innis; 5,066,584 to Gyllensten, et al; 4,889,818 to Gelfand, et al; 4,994,370 to Silver, et al; 4,766,067 to Biswas; 4,656,134 to Ringold) and RNA mediated amplification that uses anti-sense RNA to the target sequence as a template for double-stranded DNA synthesis (U.S. Patent No. 5,130,238 to Malek, et al, with the tradename NASBA), the

entire contents of which references are incorporated herein by reference. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*.)

For instance, polymerase chain reaction (PCR) technology can be used to amplify the sequences of polynucleotides of the present invention and related genes directly from genomic DNA or cDNA libraries. PCR and other in vitro amplification methods can also be useful, for example, to clone nucleic acid sequences that code for proteins to be expressed, to make nucleic acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes. Examples of techniques sufficient to direct persons of skill through in vitro amplification methods are found in Berger, *supra*, Sambrook, *supra*, and Ausubel, *supra*, as well as Mullis, et al., U.S. Patent No. 4,683,202 (1987); and Innis, et al., PCR Protocols A Guide to Methods and Applications, Eds., Academic Press Inc., San Diego, CA (1990). Commercially available kits for genomic PCR amplification are known in the art. See, e.g., Advantage-GC Genomic PCR Kit (Clontech). Additionally, e.g., the T4 gene 32 protein (Boehringer Mannheim) can be used to improve yield of long PCR products.

The isolated nucleic acids of the present invention can also be prepared by direct chemical synthesis by known methods (see, e.g., Ausubel, et al., *supra*). Chemical synthesis generally produces a single-stranded oligonucleotide, which can be converted into double-stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. One of skill in the art will recognize that while chemical synthesis of DNA can be limited to sequences of about 100 or more bases, longer sequences can be obtained by the ligation of shorter sequences.

Polynucleotides Selectively Hybridizing to a Polynucleotide as Described

As described above, the present invention provides isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides of the present invention can be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library.

Preferably, the cDNA library comprises at least 80% full-length sequences, preferably, at least 85% or 90% full-length sequences, and, more preferably, at least 95% full-length sequences. The cDNA libraries can be normalized to increase the representation of rare sequences. Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and can be employed to identify orthologous or paralogous sequences.

Optionally, polynucleotides of this invention will encode at least a portion of a protein or an antibody encoded by the polynucleotides described herein. The polynucleotides of this invention embrace nucleic acid sequences that can be employed for selective hybridization to a polynucleotide encoding a protein or an antibody of the present invention. See, e.g., Ausubel, *supra*; Colligan, *supra*,
5 each entirely incorporated herein by reference.

Use of CNGH0010 Polypeptides and Polynucleotides

The polynucleotides and polypeptides of the invention are also useful for assaying a medium for the presence of a substance that modulates CNGH0010 protein function by affecting the binding of a CNGH0010 analog protein to cellular binding partners, such as the CNGH0010 receptor.
10 Examples of modulators include polypeptides or small organic molecules.

Polypeptides of the invention may also be used to identify lead compounds for drug development. The structure of the polypeptides described herein can be readily determined by a number of methods such as NMR and X-ray crystallography. A comparison of the structures of polypeptides similar in sequence, but differing in the biological activities that they elicit in target
15 molecules can provide information about the structure-activity relationship of the target. Information obtained from the examination of structure-activity relationships can be used to design either modified polypeptides, or other small molecules or lead compounds which can be tested for predicted properties as related to the target molecule. The activity of the lead compounds can be evaluated using assays similar to those described herein.

Information about structure-activity relationships may also be obtained from co-crystallization studies. In these studies, a polypeptide with a desired activity is crystallized in association with a target molecule, and the X-ray structure of the complex is determined. The structure can then be compared to the structure of the target molecule in its native state, and information from such a comparison may be used to design compounds expected to possess desired
20 activities.
25

The invention also contemplates methods for identifying novel compounds that bind to the polypeptides of the invention thereby affecting a CNGH0010-signaling pathway. Protein-protein interactions may be identified using conventional methods such as co-immunoprecipitation, crosslinking and co-purification through gradients or chromatographic columns. Methods may also
30 be employed that result in the simultaneous identification of genes which encode proteins interacting with a molecule. These methods include probing expression libraries with labeled molecules. Additionally, x-ray crystallographic studies may be used as a means of evaluating interactions with substances and molecules.

It will be appreciated that fusion proteins and recombinant proteins may be used in the above
35 described methods. The reagents suitable for applying the methods of the invention to evaluate substances and compounds that affect or modulate a CNGH0010 signaling pathway may be packaged

into convenient kits providing the necessary materials packaged into suitable containers. The kits may also include suitable supports useful in performing the methods of the invention.

Mature CNGH0010 or its analogs can be used to modulate, *i.e.*, increase or decrease, eukaryotic cell activity and/or number, such as proliferation and activation. Moreover, mature

5 CNGH0010 or its analogs can be used to regulate cell differentiation and migration. Since CNGH0010 can be secreted, mature CNGH0010 or its analogs can also be used to treat various kinds of immune-mediated inflammatory diseases that are dependent on cell proliferation, differentiation, and migration, such as but not limited to, psoriasis, rheumatoid arthritis, emphysema, asthma, diabetes, autoimmune thyroiditis, inflammatory bowel diseases, including Crohn's disease and

10 ulcerative colitis, different types of dermatitis including allergic dermatitis, contact dermatitis, actinic keratosis, wound healing, scar formation, various renal diseases, various respiratory diseases, various diseases of reproductive organs, such as endometriosis, melanoma, squamous cell carcinoma, ovarian cancer, breast cancer, lung cancer, colon cancer, prostate cancer, renal cell carcinoma, Grave's diseases and other inflammatory and hyperproliferative diseases. In addition, mature CNGH0010 or

15 its analogs can be used to enhance immune responses to an infectious disease. Mature CNGH0010 or its analogs can be used alone or in combination with an antigen as an adjuvant to treat or prevent various infectious, hyperproliferative and inflammatory diseases.

The mode of administration for therapeutic use of the polypeptides of the invention may be any suitable route that delivers the agent to the host, such as parenteral, subcutaneous, intramuscular,

20 intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolonic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual,

25 intranasal, or transdermal.

Polypeptides of the invention may be prepared as pharmaceutical compositions containing an effective amount of the binding agent as an active ingredient in a pharmaceutically acceptable carrier. An aqueous suspension or solution containing the binding agent, preferably buffered at physiological pH, in a form ready for injection is preferred. The compositions for parenteral administration will

30 commonly comprise a solution of the binding agent of the invention or a cocktail thereof dissolved in a pharmaceutically acceptable carrier, preferably, an aqueous carrier. A variety of aqueous carriers may be employed, *e.g.*, 0.4% saline, 0.3% glycine and the like. These solutions are sterile and generally free of particulate matter. These solutions may be sterilized by conventional, well known sterilization techniques (*e.g.*, filtration). The compositions may contain pharmaceutically acceptable

35 auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, etc. The concentration of the polypeptides of the invention in such pharmaceutical formulations can vary widely, *i.e.*, from less than about 0.5%, usually at or at least about 1% to as

much as 15 or 20% by weight, and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected.

Thus, a pharmaceutical composition of the invention for intramuscular injection could be prepared to contain 1 mL sterile buffered water, and between about 1 ng to about 100 mg, *e.g.*, about 50 ng to about 30 mg or more, preferably, about 5 mg to about 25 mg, of a polypeptide of the invention. Similarly, a pharmaceutical composition of the invention for intravenous infusion could be made up to contain about 250 ml of sterile Ringer's solution, and about 1 mg to about 30 mg and preferably 5 mg to about 25 mg of a polypeptide of the invention. Actual methods for preparing parenterally administrable compositions are well known or will be apparent to those skilled in the art and are described in more detail in, for example, *Remington, the Science and Practice of Pharmacy*, 19th ed., Mack Publishing Company, Easton, Pa (1995).

The polypeptides of the invention, when in a pharmaceutical preparation, can be present in unit dose forms. The appropriate therapeutically effective dose can be determined readily by those of skill in the art. A determined dose may, if necessary, be repeated at appropriate time intervals that are selected as appropriate by a physician during the treatment period.

The polypeptides of the invention can be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional protein preparations and lyophilization and reconstitution techniques known in the art can be employed.

If a polypeptide of the present invention is to be expressed for use in screening assays, it is generally preferred that the polypeptide be produced at the surface of the cell. In this event, the cells may be harvested prior to use in the screening assay. If the polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide. If produced intracellularly, the cell must first be lysed before the polypeptide is recovered.

This invention also relates to the use of polynucleotides of the present invention as diagnostic reagents. Detection of a mutated form of the gene characterized by the polynucleotide of SEQ ID NO:2 which is associated with a dysfunction will provide a diagnostic tool that can add to, or define, a diagnosis of a disease, or susceptibility to a disease, which results from under-expression, over-expression or altered expression of the gene. Individuals carrying mutations in the gene may be detected at the DNA level by a variety of techniques.

Nucleic acids for diagnosis may be obtained from a subject's cells, such as from blood, urine, saliva, tissue biopsy or autopsy material. The genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeled CNGH0010 nucleotide sequences. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence differences may also be detected by alterations in

electrophoretic mobility of DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing (e.g., Myers et al., Science (1985) 230:1242). Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method (see Cotton et al., Proc Natl Acad Sci USA (1985) 85:4397-4401). In
5 another embodiment, an array of oligonucleotide probes comprising CNGH0010 nucleotide sequences or fragments thereof can be constructed to conduct efficient screening of e.g., genetic mutations. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics, including gene expression, genetic linkage, and genetic variability (see for example: M. Chee et al., Science, Vol 274, pp 610-613 (1996)).

10 The diagnostic assays offer a process for diagnosing or determining a susceptibility to the relevant diseases through detection of mutation in the CNGH0010 gene by the methods described. In addition, such diseases may be diagnosed by methods comprising determining from a sample derived from a subject an abnormally decreased or increased level of polypeptide or mRNA. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the
15 art for the quantitation of polynucleotides, such as, for example, nucleic acid amplification, for instance, PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such as a polypeptide of the present invention, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA
20 assays.

Thus in another aspect, the present invention relates to a diagnostic kit which comprises:

- (a) a polynucleotide of the present invention, preferably, one of the nucleotide sequences of SEQ ID NOS:2, 4, 6, 8, and 10 and variants, polynucleotides with at least 70% identity to any of SEQ ID NOS:2, 4, 6, 8, and 10 or variants, or a fragment thereof;
- 25 (b) a nucleotide sequence complementary to that of (a);
- (c) a polypeptide of the present invention, preferably, one of the polypeptides of SEQ ID NOS:3, 5, 7, 9, and 11 and variants, polypeptides with at least 70% identity to any of SEQ ID NOS:3, 5, 7, 9, and 11 and variants, or a fragment thereof; or
- (d) an antibody to a polypeptide of the present invention, variants, and fragments thereof, preferably,
30 to one of the polypeptides of SEQ ID NOS:3, 5, 7, 9, and 11 and variants.

It will be appreciated that in any such kit, components (a), (b), (c), or (d) from above may comprise a substantial component. Such a kit will be of use in diagnosing a disease or susceptibility to a disease, such as but not limited to, psoriasis, rheumatoid arthritis, emphysema, asthma, diabetes, autoimmune thyroiditis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis,
35 various types of dermatitis including allergic dermatitis, contact dermatitis, actinic keratosis, wound healing, scar formation, various renal diseases, various respiratory diseases, various diseases of reproductive organs, such as endometriosis, melanoma, squamous cell carcinoma, ovarian cancer,

breast cancer, lung cancer, colon cancer, prostate cancer, renal cell carcinoma, Grave's diseases and other inflammatory and hyperproliferative diseases.

The nucleotide sequences of the present invention are also valuable for chromosome identification. Each genomic sequence is specifically targeted to, and can hybridize with, a particular
5 location on an individual human chromosome. The mapping of relevant sequences to chromosomes according to the present invention may be useful in correlating those sequences with gene-associated diseases and conditions. Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found in, for example, V. McKusick, Mendelian Inheritance in Man (available on-line
10 through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region can then be identified through linkage analysis (i.e., coinheritance of physically adjacent genes).

The differences in the cDNA or genomic sequence between affected and unaffected individuals can also be determined. If a mutation is observed in some or all of the affected individuals
15 but not in any normal individuals, then the mutation is likely to be the causative agent of the disease. The polynucleotides, polypeptides and antibodies to the polypeptides of the present invention may also be used to configure screening methods for detecting the effect of added compounds on the production of mRNA and polypeptide in cells. For example, an ELISA assay may be constructed for measuring secreted or cell-associated levels of polypeptide using monoclonal and polyclonal
20 antibodies by standard methods known in the art. This can be used to discover agents that may inhibit or enhance the production of polypeptide (also called antagonist or agonist, respectively) from suitably manipulated cells or tissues.

The polypeptide may be used to identify membrane bound or soluble receptors, if any, through standard receptor binding techniques known in the art. These include, but are not limited to,
25 ligand binding and crosslinking assays in which the polypeptide is labeled with a radioactive isotope (for instance, ^{125}I), chemically modified (for instance, biotinylated), or fused to a peptide sequence suitable for detection or purification, and incubated with a source of the putative receptor (cells, cell membranes, cell supernatants, tissue extracts, bodily fluids). Other methods include biophysical techniques, such as surface plasmon resonance and spectroscopy. These screening methods may also
30 be used to identify agonists and antagonists of the polypeptide that compete with the binding of the polypeptide to its receptors, if any. Standard methods for conducting these assays are well understood in the art.

Examples of potential polypeptide antagonists include antibodies or, in some cases, oligonucleotides or proteins which are closely related to the ligands, substrates, receptors, enzymes,
35 etc., of the polypeptide. For example, a fragment of the ligands, substrates, receptors, enzymes, etc.;

or small molecules may bind to the polypeptide of the present invention but may not elicit a response, i.e., to the activity of the polypeptide.

Thus in another aspect, the present invention relates to a screening kit for identifying agonists, antagonists, ligands, receptors, substrates, enzymes, etc. for polypeptides of the present invention; or compounds which decrease or enhance the production of such polypeptides, which comprises:

- (a) a polypeptide of the present invention;
- (b) a recombinant cell expressing a polypeptide of the present invention;
- (c) a cell membrane expressing a polypeptide of the present invention; or
- (d) antibody to a polypeptide of the present invention, which polypeptide is preferably one of SEQ ID NOS:3, 5, 7, 9, and 11 or splice variants.

It will be appreciated that in any such kit, components (a), (b), (c), or (d) may comprise a substantial component.

It will be readily appreciated by the skilled artisan that a polypeptide of the present invention may also be used in a method for the structure-based design of an agonist, antagonist or inhibitor of the polypeptide, by:

- (a) determining in the first instance the three-dimensional structure of the polypeptide;
- (b) deducing the three-dimensional structure for the likely reactive or binding site(s) of an agonist, antagonist or inhibitor;
- (c) synthesizing candidate compounds that are predicted to bind to or react with the deduced binding or reactive site; and
- (d) testing whether the candidate compounds are indeed agonists, antagonists or inhibitors.

It will be further appreciated that this will normally be an interactive process.

Polypeptides used in treatment can also be generated endogenously in the subject, in treatment modalities often referred to as "gene therapy" as described above. Thus, for example, cells from a subject may be engineered with a polynucleotide, such as a DNA or RNA, to encode a polypeptide ex vivo, and for example, by the use of retroviral plasmid vector. The cells are then introduced into the subject.

Anti-CNGH0010 Antibodies

An antibody of the invention binds at least one specified epitope specific to a CNGH0010 protein, subunit, fragment, portion of the invention, or any combination thereof. The epitope can comprise an antibody binding region that comprises at least one portion of the amino acid sequence of SEQ ID NOS:3, 5, 7, 9, and 11 or its variants (e.g., splice variants described below), which epitope is preferably comprised of at least 1-5 amino acids of the sequences. The antibody can include or be derived from any mammal, such as, but not limited to, a human, a mouse, a rabbit, a rat, a rodent, a primate, or any combination thereof, and the like.

An anti-CNGH0010 antibody, as described herein, has at least one activity, such as, but not limited to neutralizing CNGH0010-dependent receptor phosphorylation, receptor internalization, cell adhesion, migration and invasion, and induction of signaling molecules or adaptation of cell markers. An anti-CNGH0010 antibody can thus be screened for a corresponding activity according to known methods, such as but not limited to, at least one biological activity of human CNGH0010. The antibody can be used to measure or affect a cell, tissue, organ or animal (including mammals and humans), to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one CNGH0010-related disease or condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified CNGH0010-related condition.

Definition & Characterization of an anti-CNGH0010 Antibody

As used herein, an "anti-CNGH0010 antibody," "anti-CNGH0010 antibody portion," or "anti-CNGH0010 antibody fragment" and/or "anti-CNGH0010 antibody variant" and the like include any protein or polypeptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to, at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, or at least one portion of a CNGH0010 receptor or binding protein derived from a CNGH0010 protein or polypeptide of the invention, which can be incorporated into an antibody of the present invention. Such antibody optionally further affects a specific ligand, such as but not limited to, where such antibody modulates, decreases, increases, antagonizes, angonizes, mitigates, alleviates, blocks, inhibits, abrogates and/or interferes with at least one CNGH0010 activity or binding, or with CNGH0010 ligand activity or binding, in vitro, in situ and/or in vivo. As a non-limiting example, a suitable anti-CNGH0010 antibody, specified portion or variant of the present invention can bind at least one CNGH0010 protein or polypeptide of the invention, or specified portions, variants or domains thereof. A suitable anti-CNGH0010 antibody, specified portion, or variant can also optionally affect at least one of CNGH0010 activity or function, such as but not limited to, RNA, DNA or protein synthesis, CNGH0010 release, CNGH0010 receptor signaling, CNGH0010 activity, CNGH0010 production and/or synthesis.

The term "antibody" is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian CNGH0010. For example, antibody fragments capable of binding to CNGH0010 or portions thereof, including, but not limited to, Fab (e.g., by papain

digestion), Fab' (e.g., by pepsin digestion and partial reduction) and F(ab')₂ (e.g., by pepsin digestion), facb (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, Immunology, *supra*).

5 Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a F(ab')₂ heavy chain portion can be designed to include DNA sequences encoding the CH₁ domain and/or hinge region of
10 the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques.

As used herein, the term "human antibody" refers to an antibody in which substantially every part of the protein (e.g., CDR, framework, CL, CH domains (e.g., CH₁, CH₂, CH₃), hinge, (VL, VH))
15 is substantially non-immunogenic in humans, with only minor sequence changes or variations. Similarly, antibodies designated primate (monkey, baboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pig, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies of the invention can include any combination of the above. Such changes or variations optionally and preferably retain or
20 reduce the immunogenicity in humans or other species relative to non-modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human antibody is a single chain antibody, it can comprise a linker peptide
25 that is not found in native human antibodies. For example, a Fv can comprise a linker peptide, such as 2 to about 8 glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

The isolated antibodies of the present invention comprise any isolated or prepared antibody
30 prepared as described herein. Preferably, the human antibody or antigen-binding fragment binds human CNGH0010 and, thereby, partially or substantially neutralizes at least one biological activity of the protein. An antibody, or specified portion or variant thereof, that partially or preferably substantially neutralizes at least one biological activity of at least one CNGH0010 protein or fragment can bind the protein or fragment and thereby inhibit activities mediated through the binding of
35 CNGH0010 to the CNGH0010 receptor or through other CNGH0010-dependent or mediated mechanisms. As used herein, the term "neutralizing antibody" refers to an antibody that can inhibit a CNGH0010-dependent activity by about 20-120%, preferably by at least about 10, 20, 30, 40, 50, 55,

60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% or more depending on the assay. The capacity of an anti-CNGH0010 antibody to inhibit a CNGH0010-dependent activity is preferably assessed by at least one suitable CNGH0010 protein or receptor assay, as described herein and/or as known in the art. A human antibody of the invention can be of any class (IgG, IgA, IgM, IgE, IgD, etc.) or isotype and can comprise a kappa or lambda light chain. In one embodiment, the human antibody comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. Antibodies of this type can be prepared by employing a transgenic mouse or other transgenic non-human mammal comprising at least one human light chain (e.g., IgG, IgA and IgM (e.g., $\gamma 1$, $\gamma 2$, $\gamma 3$, $\gamma 4$) transgenes as described herein and/or as known in the art. In another embodiment, the anti-human CNGH0010 human antibody comprises an IgG1 heavy chain and an IgG1 light chain.

At least one antibody of the invention binds to at least one specified epitope specific to at least one CNGH0010 protein, subunit, fragment, portion or any combination thereof, as described herein. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of the protein sequences corresponding to the peptide sequences from the receptor binding region of human CNGH0010, as described herein, which epitope is preferably comprised of at least one extracellular, soluble, hydrophilic, external or cytoplasmic portion of the protein.

Generally, the human antibody or antigen-binding fragment of the present invention will comprise an antigen-binding region that comprises at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one heavy chain variable region and at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one light chain variable region.

Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, preferably, human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for at least one CNGH0010 protein of the invention, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, U.S. Patent Nos. 6210668, 6193967, 6132992, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 5807706, 5643759, 5601819, 5582996, 5496549, and 4676980, WO 91/00360, WO 92/00373, EP

03089, Traunecker et al., EMBO J. 10:3655 (1991), and Suresh et al., Methods in Enzymology 121:210 (1986), each entirely incorporated herein by reference.

Anti-CNGH0010 antibodies useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to CNGH0010 and, optionally and preferably, having low toxicity. In particular, an antibody, specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably, possess low immunogenicity, is useful in the present invention. The antibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably, less than about 100 measured with a double antigen enzyme immunoassay) (Elliott et al., Lancet 344:1125-1127 (1994), entirely incorporated herein by reference).

Application of the anti-CNGH0010 antibody can comprise administering an effective amount of a composition or a pharmaceutical composition comprising at least one anti-CNGH0010 antibody to a cell, tissue, organ, animal, or patient in need of such modulation, treatment, alleviation, prevention, or reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.001 to 500 mg/kg per single (e.g., bolus), multiple or continuous administration, or to achieve a serum concentration of 0.01-5000 µg/ml serum concentration per single, multiple, or continuous administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

As those of skill will appreciate, the present invention includes at least one biologically active antibody of the present invention. Biologically active antibodies have a specific activity at least 20%, 30%, or 40%, and, preferably, at least 50%, 60%, or 70%, and, most preferably, at least 80%, 90%, or 95%-100% of that of the native (non-synthetic), endogenous or related and known antibody. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity are well known to those of skill in the art.

In another aspect, the invention relates to human antibodies and antigen-binding fragments, as described herein, which are modified by the covalent attachment of an organic moiety. Such modification can produce an antibody or antigen-binding fragment with improved pharmacokinetic properties (e.g., increased in vivo serum half-life). The organic moiety can be a linear or branched hydrophilic polymeric group, fatty acid group, or fatty acid ester group. Lipid molecules such as a disteroylphosphatidyl ethanolamine moiety, either alone or covalently bonded to a hydrophilic polymer, are useful. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g.,

polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrrolidone, and the fatty acid or fatty acid ester group can comprise from about eight to about forty carbon atoms.

The modified antibodies and antigen-binding fragments of the invention can comprise one or more organic moieties that are covalently bonded, directly or indirectly, to the antibody. Each organic moiety that is bonded to an antibody or antigen-binding fragment of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, an antibody modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like), carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine, polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrrolidone. Preferably, the hydrophilic polymer that modifies the antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example, PEG₅₀₀₀ and PEG_{20,000}, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying antibodies of the invention include, for example, n-dodecanoate (C12, laurate), n-tetradecanoate (C14, myristate), n-octadecanoate (C18, stearate), n-eicosanoate (C20, arachidate), n-docosanoate (C22, behenate), n-triacontanoate (C30), n-tetracontanoate (C40), cis- Δ^9 -octadecanoate (C18, oleate), all cis- $\Delta^{5,8,11,14}$ -eicosatetraenoate (C20, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably, one to about six, carbon atoms.

The modified human antibodies and antigen-binding fragments can be prepared using suitable methods, such as by reaction with one or more modifying agents. A "modifying agent" as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid

ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acryloyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example, a divalent C1-C12 group wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, $-(CH_2)_3-$, $-NH-(CH_2)_6-NH-$, $-(CH_2)_2-NH-$ and $-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH-NH-$. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for example, Thompson, et al., WO 92/16221, the entire teachings of which are incorporated herein by reference.)

The modified antibodies of the invention can be produced by reacting a human antibody or antigen-binding fragment with a modifying agent. For example, the organic moieties can be bonded to the antibody in a non-site specific manner by employing an amine-reactive modifying agent, for example, a NHS ester of PEG. Modified human antibodies or antigen-binding fragments can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of an antibody or antigen-binding fragment. The reduced antibody or antigen-binding fragment can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified human antibodies and antigen-binding fragments comprising an organic moiety that is bonded to specific sites of an antibody of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch et al., *Bioconjugate Chem.*, 3:147-153 (1992); Werlen et al., *Bioconjugate Chem.*, 5:411-417 (1994); Kumaran et al., *Protein Sci.* 6(10):2233-2241 (1997); Itoh et al., *Bioorg. Chem.*, 24(1): 59-68 (1996); Capellas et al., *Biotechnol. Bioeng.*, 56(4):456-463 (1997)), and the methods described in Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).

Generation of Monoclonal Antibodies

Monoclonal antibodies of this invention may be raised by traditional immunization and hybridoma technology. After immunization of mice with human CNGH0010 antigenic compositions comprising the polypeptides of the invention, spleen cells or lymphocytes from lymph node tissue from immunized animals are recovered and immortalized by fusion with myeloma cells or by Epstein-Barr (EB)-virus transformation. Monoclonal antibodies are obtained by screening for clones expressing the desired antibody. While mice are frequently employed as the test model, it is contemplated that any mammalian subject, including human subjects or antibody-producing cells, can be manipulated according to the processes of this invention to serve as the basis for production of mammalian, including human and hybrid cell lines. Techniques for cloning recombinant DNA of antibody molecule directly from an antibody-expressing B cell are within the scope of this invention. Such B cells can be isolated by the fluorescence activated cell sorter.

While routinely, mouse monoclonal antibodies are generated, the invention is not so limited. For therapeutic applications, human or humanized antibodies are desired. Such antibodies can be obtained by using human hybridomas or by generating humanized antibodies. Humanized antibodies can be developed by replacing the specific segments of a non-human antibody with corresponding segments of a human antibody gene. This process retains most or all of CDR regions of the light and heavy chain variable regions of parental antibody and largely replaces the framework regions with human sequences [EP Patent No. 184187; EP Patent No. 171496; EP Patent No. 173494 and WO Patent No. 86/01533]. Human monoclonal antibodies are also generated in transgenic mice that contain genes or gene segments encoding human antibodies in their genome [U.S. Patent No. 6,162,963; WO Patent No. 93/12227; U.S. Patent No. 5,877,5397; U.S. Patent No. 5,874,299; U.S. Patent No. 5,814,318; U.S. Patent No. 5,789,650; U.S. Patent No. 5,770,429; U.S. Patent No. 5,661,016; U.S. Patent No. 5,625,126; U.S. Patent No. 5,569,825; U.S. Patent No. 5,545,806; and WO Patent No. 91/10741].

Human monoclonal antibodies are also obtained from recombinant antibody libraries, generated in vitro or in vivo, using phage display, ribosome display, or related screening or selection techniques. Examples of procedures for generating antibody libraries, primarily of human origin, are disclosed by A. Knappik and others [65] [U.S. Patent No. 6,291,158; U.S. Patent No. 6,291,159; U.S. Patent No. 6,291,160 and U.S. Patent No. 6,291,161]. Examples of methods for selections of human antibodies to specific antigen targets from such libraries are disclosed by B. Krebs and others [66] [U.S. Patent No. 5,955,341; U.S. Patent No. 5,759,817; U.S. Patent No. 5,658,727; U.S. Patent No. 6,235,469; U.S. Patent No. 5,969,108; U.S. Patent No. 5,886,793].

Detailed Description of Methods to Generate anti-CNGH0010 Antibodies

At least one anti-CNGH0010 antibody of the present invention can be optionally produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as well known in the art. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), each entirely incorporated herein by reference.

Human antibodies that are specific for human CNGH0010 proteins (as described herein), variants, or fragments thereof can be raised against an appropriate immunogenic antigen as described herein, such as the isolated and/or CNGH0010 proteins, variants, or portions thereof (including synthetic molecules, such as synthetic polypeptides) as described herein. Other specific or general mammalian antibodies can be similarly raised. Preparation of immunogenic antigens, and monoclonal antibody production can be performed using any suitable technique.

In one approach, a hybridoma is produced by fusing a suitable immortal cell line, e.g., a myeloma cell line such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1, L.5, >243, P3X63Ag8.653, Sp2 SA3, Sp2 MAI, Sp2 SS1, Sp2 SA5, U937, MLA 144, ACT IV, MOLT4, DA-1, JURKAT, WEHI, K-562, COS, RAJI, NIH 3T3, HL-60, MLA 144, NAMAIWA, NEURO 2A, or the like, heteromyelomas, fusion products thereof, any cell or fusion cell derived therefrom, or any other suitable cell line as known in the art (See, e.g., www.atcc.org, www.lifetech.com., and the like), with antibody producing cells, such as, but not limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell containing cells, or any other cells expressing heavy or light chain constant or variable or framework or CDR sequences, either as endogenous or heterologous nucleic acid, as recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian, fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA, cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA, tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof. See, e.g., Ausubel, *supra*, and Colligan, Immunology, *supra*, chapter 2, entirely incorporated herein by reference.

Antibody producing cells can also be obtained from the peripheral blood or, preferably the spleen or lymph nodes, of humans or other suitable animals that have been immunized with the antigen of interest. Any other suitable host cell can also be used for expressing heterologous or endogenous nucleic acid encoding an antibody, specified fragment or variant thereof, of the present invention. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods. Cells that produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).

Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a polypeptide or protein display library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, RNA, cDNA, or the like, display library; e.g., as available from Cambridge antibody Technologies, Cambridgeshire, UK; MorphoSys, Martinsreid/Planegg, DE; Biovation, Aberdeen, Scotland, UK; BioInvent, Lund, Sweden; Dyax Corp., Enzon, Affymax/Biosite; Xoma, Berkeley, CA; Ixsys. See, e.g., EP 368,684, PCT/GB91/01134; PCT/GB92/01755; PCT/GB92/002240; PCT/GB92/00883; PCT/GB93/00605; U.S. 08/350260(5/12/94); PCT/GB94/01422; PCT/GB94/02662; PCT/GB97/01835; (CAT/MRC); WO90/14443; WO90/14424; WO90/14430; PCT/US94/1234; WO92/18619; WO96/07754; (Scripps); WO96/13583, WO97/08320 (MorphoSys); WO95/16027 (BioInvent); WO88/06630; WO90/3809 (Dyax); U.S. 4,704,692 (Enzon); PCT/US91/02989 (Affymax); WO89/06283; EP 371 998; EP 550 400; (Xoma); EP 229 046; PCT/US91/07149 (Ixsys); or stochastically generated peptides or proteins - U.S. 5723323, 5763192, 5814476, 5817483, 5824514, 5976862, WO 86/05803, EP 590 689 (Ixsys, now Applied Molecular Evolution (AME), each entirely incorporated herein by reference) or that rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al., Microbiol. Immunol. 41:901-907 (1997); Sandhu et al., Crit. Rev. Biotechnol. 16:95-118 (1996); Eren et al., Immunol. 93:154-161 (1998), each entirely incorporated by reference as well as related patents and applications) that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein. Such techniques, include, but are not limited to, ribosome display (Hanes et al., Proc. Natl. Acad. Sci. USA, 94:4937-4942 (May 1997); Hanes et al., Proc. Natl. Acad. Sci. USA, 95:14130-14135 (Nov. 1998)); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (U.S. Patent No. 5,627,052, Wen et al., J. Immunol. 17:887-892 (1987); Babcook et al., Proc. Natl. Acad. Sci. USA 93:7843-7848 (1996)); gel microdroplet and flow cytometry (Powell et al., Biotechnol. 8:333-337 (1990); One Cell Systems, Cambridge, MA; Gray et al., J. Imm. Meth. 182:155-163 (1995); Kenny et al., Bio/Technol. 13:787-790 (1995)); B-cell selection (Steenbakkers et al., Molec. Biol. Reports 19:125-134 (1994); Jonak et al., Progress Biotech, Vol. 5, In Vitro Immunization in Hybridoma Technology, Borrebaeck, ed., Elsevier Science Publishers B.V., Amsterdam, Netherlands (1988)).

Methods for engineering or humanizing non-human or human antibodies can also be used and are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid residues from a source that is non-human, e.g., but not limited to, mouse, rat, rabbit, non-human primate or other mammal. These human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence. Known human Ig sequences are disclosed, e.g., at

www.ncbi.nlm.nih.gov/entrez/query.fcgi; www.atcc.org/phage/hdb.html; www.sciquest.com/; www.abcam.com/; www.antibodyresource.com/onlinecomp.html; www.public.iastate.edu/~pedro/research_tools.html; www.mgen.uni-heidelberg.de/SD/IT/IT.html;

- www.whfreeman.com/immunology/CH05/kuby05.htm;
 www.library.thinkquest.org/12429/Immune/Antibody.html;
 www.hhmi.org/grants/lectures/1996/vlab/; www.path.cam.ac.uk/~mrc7/mikeimages.html;
 www.antibodyresource.com/;
- 5 mcb.harvard.edu/BioLinks/Immunology.html.www.immunologylink.com/;
 pathbox.wustl.edu/~hcenter/index.html; www.biotech.ufl.edu/~hcl/;
 www.pebio.com/pa/340913/340913.html; www.nal.usda.gov/awic/pubs/antibody/;
 www.m.ehime-u.ac.jp/~yasuhito/Elisa.html; www.biodesign.com/table.asp;
 www.icnet.uk/axp/facs/davies/links.html; www.biotech.ufl.edu/~fccl/protocol.html; www.isac-
- 10 net.org/sites_geo.html; aximt1.imt.uni-marburg.de/~rek/AEPStart.html;
 baserv.uci.kun.nl/~jraats/links1.html; www.recab.uni-hd.de/immuno.bme.nwu.edu/; www.mrc-
 cpe.cam.ac.uk/imt-doc/public/INTRO.html; www.ibt.unam.mx/vir/V_mice.html; imgt.cnusc.fr:8104/;
 www.biochem.ucl.ac.uk/~martin/abs/index.html; antibody.bath.ac.uk/;
 abgen.cvm.tamu.edu/lab/wwwabgen.html; www.unizh.ch/~honegger/AHOseminar/Slide01.html;
- 15 www.cryst.bbk.ac.uk/~ubcg07s/; www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm;
 www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html;
 www.ibt.unam.mx/vir/structure/stat_aim.html; www.biosci.missouri.edu/smithgp/index.html;
 www.cryst.bioc.cam.ac.uk/~fmolina/Web-pages/Pept/spottech.html; www.jerini.de/fr_products.htm;
 www.patents.ibm.com/ibm.html.Kabat et al., Sequences of Proteins of Immunological Interest, U.S.
- 20 Dept. Health (1983), each entirely incorporated herein by reference.

Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art. Generally part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions are replaced with

25 human or other amino acids. Antibodies can also optionally be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, humanized antibodies can be optionally prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to

30 those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the

35 consensus and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding. Humanization or engineering of antibodies of the present

invention can be performed using any known method, such as but not limited to, those described in, Winter (Jones et al., *Nature* 321:522 (1986); Riechmann et al., *Nature* 332:323 (1988); Verhoeyen et al., *Science* 239:1534 (1988)), Sims et al., *J. Immunol.* 151: 2296 (1993); Chothia and Lesk, *J. Mol. Biol.* 196:901 (1987), Carter et al., *Proc. Natl. Acad. Sci. U.S.A.* 89:4285 (1992); Presta et al., *J. Immunol.* 151:2623 (1993), U.S. Patent Nos: 5723323, 5976862, 5824514, 5817483, 5814476, 5763192, 5723323, 5,766886, 5714352, 6204023, 6180370, 5693762, 5530101, 5585089, 5225539; and 4816567, PCT/: US98/16280, US96/18978, US91/09630, US91/05939, US94/01234, GB89/01334, GB91/01134, GB92/01755; WO90/14443, WO90/14424, WO90/14430, and EP 229246, each entirely incorporated herein by reference, included references cited therein.

10 The anti-CNGH0010 antibody can also be optionally generated by immunization of a transgenic animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of producing a repertoire of human antibodies, as described herein and/or as known in the art. Cells that produce a human anti-CNGH0010 antibody can be isolated from such animals and immortalized using suitable methods, such as the methods described herein.

15 Transgenic mice that can produce a repertoire of human antibodies that bind to human antigens can be produced by known methods (e.g., but not limited to, U.S. Pat. Nos. 5,770,428, 5,569,825, 5,545,806, 5,625,126, 5,625,825, 5,633,425, 5,661,016 and 5,789,650 issued to Lonberg et al.; Jakobovits et al. WO 98/50433, Jakobovits et al. WO 98/24893, Lonberg et al. WO 98/24884, Lonberg et al. WO 97/13852, Lonberg et al. WO 94/25585, Kucherlapate et al. WO 96/34096, Kucherlapate et al. EP 0463 151 B1, Kucherlapate et al. EP 0710 719 A1, Surani et al. U.S. Pat. No. 5,545,807, Bruggemann et al. WO 90/04036, Bruggemann et al. EP 0438 474 B1, Lonberg et al. EP 0814 259 A2, Lonberg et al. GB 2 272 440 A, Lonberg et al. *Nature* 368:856-859 (1994), Taylor et al., *Int. Immunol.* 6(4):579-591 (1994), Green et al, *Nature Genetics* 7:13-21 (1994), Mendez et al., *Nature Genetics* 15:146-156 (1997), Taylor et al., *Nucleic Acids Research* 20(23):6287-6295 (1992), 20 Tuailon et al., *Proc Natl Acad Sci USA* 90(8):3720-3724 (1993), Lonberg et al., *Int Rev Immunol* 13(1):65-93 (1995) and Fishwald et al., *Nat Biotechnol* 14(7):845-851 (1996), which are each entirely incorporated herein by reference). Generally, these mice comprise at least one transgene comprising DNA from at least one human immunoglobulin locus that is functionally rearranged, or which can undergo functional rearrangement. The endogenous immunoglobulin loci in such mice can be 25 disrupted or deleted to eliminate the capacity of the animal to produce antibodies encoded by endogenous genes.

Screening antibodies for specific binding to similar proteins or fragments can be conveniently achieved using peptide display libraries. This method involves the screening of large collections of peptides for individual members having the desired function or structure. Antibody screening of 35 peptide display libraries is well known in the art. The displayed peptide sequences can be from 3 to 5,000 or more amino acids in length, frequently from 5-100 amino acids long, and often from about 8 to 25 amino acids long. In addition to direct chemical synthetic methods for generating peptide

libraries, several recombinant DNA methods have been described. One type involves the display of a peptide sequence on the surface of a bacteriophage or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular displayed peptide sequence. Such methods are described in PCT Patent Publication Nos. 91/17271, 91/18980, 91/19818, and 93/08278. Other systems for
5 generating libraries of peptides have aspects of both in vitro chemical synthesis and recombinant methods. See, PCT Patent Publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754 and 5,643,768. Peptide display libraries, vector, and screening kits are commercially available from such suppliers as Invitrogen (Carlsbad, CA), and Cambridge antibody Technologies (Cambridgeshire, UK). See, e.g., U.S. Pat. Nos. 4704692, 4939666, 4946778, 5260203, 5455030,
10 5518889, 5534621, 5656730, 5763733, 5767260, 5856456, assigned to Enzon; 5223409, 5403484, 5571698, 5837500, assigned to Dyax, 5427908, 5580717, assigned to Affymax; 5885793, assigned to Cambridge antibody Technologies; 5750373, assigned to Genentech, 5618920, 5595898, 5576195, 5698435, 5693493, and 5698417, assigned to Xoma, Colligan, *supra*; Ausubel, *supra*; or Sambrook, *supra*, each of the above patents and publications entirely incorporated herein by reference.

15 Antibodies of the present invention can also be prepared in milk by administering at least one anti-CNGH0010 antibody encoding nucleic acid to transgenic animals or mammals, such as goats, cows, horses, sheep, and the like, that produce antibodies in their milk. Such animals can be provided using known methods. See, e.g., but not limited to, U.S. Patent Nos. 5,827,690; 5,849,992; 4,873,316; 5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely
20 incorporated herein by reference.

Antibodies of the present invention can additionally be prepared using at least one anti-CNGH0010 antibody encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to, tobacco and maize) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves
25 expressing recombinant proteins have been successfully used to provide large amounts of recombinant proteins, e.g., using an inducible promoter. See, e.g., Cramer et al., Curr. Top. Microbol. Immunol. 240:95-118 (1999) and references cited therein. Also, transgenic maize has been used to express mammalian proteins at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al.,
30 Adv. Exp. Med. Biol. 464:127-147 (1999) and references cited therein. Antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al., Plant Mol. Biol. 38:101-109 (1998) and reference cited therein. Thus, antibodies of the present invention can also be produced using transgenic plants, according to known methods. See also, e.g., Fischer et
35 al., Biotechnol. Appl. Biochem. 30:99-108 (Oct., 1999), Ma et al., Trends Biotechnol. 13:522-7 (1995); Ma et al., Plant Physiol. 109:341-6 (1995); Whitelam et al., Biochem. Soc. Trans. 22:940-944

(1994); and references cited therein. Each of the above references is entirely incorporated herein by reference.

The antibodies of the invention can bind human CNGH0010 with a wide range of affinities (KD). In a preferred embodiment, at least one human mAb of the present invention can optionally
5 bind human CNGH0010 with high affinity. For example, a human mAb can bind human CNGH0010 with a KD equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) $\times 10^{-7}$, 10^{-8} , 10^{-9} , 10^{-10} , 10^{-11} , 10^{-12} , 10^{-13} or any range or value therein.

The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, et al., "Antibody-Antigen Interactions," In
10 Fundamental Immunology, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis Immunology, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., K_D , K_a , K_d) are preferably made with standardized solutions of antibody and
15 antigen, and a standardized buffer, such as the buffer described herein.

Purification of an Antibody

An anti-CNGH0010 antibody can be recovered and purified from recombinant cell cultures by well-known methods including, but not limited to, protein A purification, ammonium sulfate or
20 ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, Current Protocols in Immunology, or Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001), e.g., Chapters 1, 4, 6, 8, 9,
25 10, each entirely incorporated herein by reference.

Antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the antibody of the present invention can be
30 glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, *supra*, Sections 17.37-17.42; Ausubel, *supra*, Chapters 10, 12, 13, 16, 18 and 20, Colligan, Protein Science, *supra*, Chapters 12-14, all entirely incorporated herein by reference.

Cloning and Expression of anti-CNGH0010 Antibody in Mammalian Cells

35 A typical mammalian expression vector contains at least one promoter element, which mediates the initiation of transcription of mRNA, the antibody coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include

enhancers, Kozak sequences, and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRS) from Retroviruses, e.g., GAS-6, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pIRES1neo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clontech Labs, Palo Alto, CA), pcDNA3.1 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pGAS-6cat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Mammalian host cells that could be used include human Hela 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the gene can be expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded antibody. The DHFR (dihydrofolate reductase) marker is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy, et al., Biochem. J. 227:277-279 (1991); Bebbington, et al., Bio/Technology 10:169-175 (1992)). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of antibodies.

The expression vectors pC1 and pC4 contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment of the CMV-enhancer (Boshart, et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

Anti-Idiotypic Antibodies to Anti-CNGH0010 Antibody Compositions

In addition to monoclonal or chimeric anti-CNGH0010 antibodies, the present invention is also directed to an anti-idiotypic (anti-Id) antibody specific for such antibodies of the invention. An anti-Id antibody is an antibody that recognizes unique determinants generally associated with the antigen-binding region of another antibody. The anti-Id can be prepared by immunizing an animal of the same species and genetic type (e.g., mouse strain) as the source of the Id antibody with the antibody or a CDR containing region thereof. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody and produce an anti-Id antibody. The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-anti-Id antibody.

CNGH0010 Polypeptide or Antibody Compositions

The present invention also provides CNGH0010 polypeptide or CNGH0010 antibody compositions comprising at least one CNGH0010 polypeptide or CNGH0010 antibodies as described herein that are provided in a non-naturally occurring composition, mixture or form. Such compositions comprise non-naturally occurring compositions comprising at least one or two full length, C- and/or N-terminally deleted variants, domains, fragments, or specified variants, of the CNGH0010 polypeptide amino acid sequence selected from the group consisting of 80-100% of the contiguous amino acids of SEQ ID NOS:3, 5, 7, 9, and 11, or CNGH0010 antibody or specified fragments, domains or variants thereof, optionally, in combination with a pharmaceutically acceptable carrier or diluent.

CNGH0010 polypeptides or antibody compounds, compositions or combinations of the present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (Easton, PA) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the anti-CNGH0010 antibody, fragment or variant composition as well known in the art or as described herein.

Pharmaceutical excipients and additives useful in the present composition include, but are not limited to, proteins, polypeptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody

components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is glycine.

Carbohydrate excipients suitable for use in the invention include, for example,
5 monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate excipients for use in the present invention are mannitol, trehalose, and raffinose.

10 Anti-CNGH0010 polypeptide or antibody compositions can also include a buffer or a pH-adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts, such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts such as
15 citrate.

Additionally, anti-CNGH0010 antibody compositions of the invention can include polymeric excipients/additives, such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl- β -cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as
20 "TWEEN 20" and "TWEEN 80"), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

These and additional known pharmaceutical excipients and/or additives suitable for use in the anti-CNGH0010 antibody, portion or variant compositions according to the invention are known in the art, e.g., as listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams &
25 Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are entirely incorporated herein by reference. Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and buffers (e.g., citrate) or polymeric agents.

Anti-CNGH0010 antibody compositions of the present invention can further comprise at least
30 one of any suitable and effective amount of a composition or pharmaceutical composition comprising at least one anti-CNGH0010 antibody contacting or administering to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally, further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist), an
35 antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local

anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limited to, any of the interleukins from IL-1 to IL-29. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., *Pharmacotherapy Handbook*, 2nd Edition, Appleton and Lange, Stamford, CT (2000); *PDR Pharmacopoeia*, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

Such anti-cancer or anti-infectives can also include toxin molecules that are associated, bound, co-formulated or co-administered with at least one antibody of the present invention. The toxin can optionally act to selectively kill the pathologic cell or tissue. The pathologic cell can be a cancer or other cell. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of ricin, diphtheria toxin, a venom toxin, or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), *Staphylococcal* enterotoxin A (SEA), B (SEB), or C (SEC), *Streptococcal* enterotoxins and the like. Such bacteria include, but are not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype O157:H7), *Staphylococcus* species (e.g., *Staphylococcus aureus*, *Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi*, *Salmonella cholerae-suis*, *Salmonella enteritidis*), *Clostridium* species (e.g., *Clostridium perfringens*, *Clostridium difficile*, *Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni*, *Camphlobacter fetus*), *Helicobacter* species, (e.g., *Helicobacter pylori*), *Aeromonas* species (e.g., *Aeromonas sobria*, *Aeromonas hydrophila*, *Aeromonas*

caviae), *Pleisomonas shigelloides*, *Yersinia enterocolitica*, *Vibrios* species (e.g., *Vibrios cholerae*, *Vibrios parahemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., *INTERNAL MEDICINE*, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., *Bacterial Infections of Humans: Epidemiology and Control*, 2d. Ed., pp 239-254, Plenum Medical Book Co., New York (1991); Mandell et al, *Principles and Practice of Infectious Diseases*, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, *FEMS Microbiology Immunology*, 76:121-134 (1991); Marrack et al, *Science*, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference.

10 **Applications**

The present invention provides a method for modulating or treating at least one CNGH0010 related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one CNGH0010 polypeptide or CNGH0010 antibody of the present invention.

15 Compositions of CNGH0010 binding polypeptides or CNGH0010 antibody or polypeptide antagonists may find therapeutic use in the treatment of disease conditions such as cancer or other human diseases with deregulated matrix production and remodeling, including lung fibrosis, liver cirrhosis, osteoporosis, rheumatoid arthritis, and asthma. Potential disease indications may also include diseases with defects in cell mechanics, tissue structure, or deregulation of mechanochemical conversion caused by pathological alteration of matrix (Ingber D., *Mechanobiology and diseases of mechanotransduction*, *Annals of Medicine*, in press).

20 The present invention also provides a method for modulating or treating at least one immune related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, iridocyclitis/uveitis/optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis/wegener's granulomatosis, sarcoidosis, orchitis/vasectomy reversal procedures, allergic/atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma/hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, diabetes, nephrosis, atopic diseases, hypersensitivity reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphylaxis, dermatitis, pernicious anemia, hemolytic disease, thrombocytopenia, graft rejection of any organ or tissue, kidney transplant rejection, heart transplant

rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, anti-receptor hypersensitivity reactions, Graves disease, Raynaud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-mediated cytotoxicity, type III hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary biliary cirrhosis, vitiligo, vasculitis, post-MI cardiomyopathy syndrome, type IV hypersensitivity, contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic/idiopathic, Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hemophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, okt3 therapy, anti-cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited to asthenia, anemia, cachexia, and the like), chronic salicylate intoxication, and the like. See, e.g., the Merck Manual, 12th-17th Editions, Merck & Company, Rahway, NJ (1972, 1977, 1982, 1987, 1992, 1999), Pharmacotherapy Handbook, Wells et al., eds., Second Edition, Appleton and Lange, Stamford, Conn. (1998, 2000), each entirely incorporated by reference.

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), chronic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodysplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignant lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, adenocarcinomas, sarcomas, malignant melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, and the like.

Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one anti-CNGH0010 antibody to a cell, tissue, organ, animal, or patient in need of such modulation, treatment or therapy. Such a method

can optionally further comprise co-administration or combination therapy for treating such immune diseases, wherein the administration of the CNGH0010 polypeptide or CNGH0010 antibody, specified portion or variant thereof, further comprises administering, before concurrently, and/or after, at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF antibody or

5 fragment, a soluble TNF receptor or fragment, fusion proteins thereof, or a small molecule TNF antagonist), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalazine), a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an

10 antiparasitic, an antiviral, a carbapenem, cephalosporin, a fluroquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteroid, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropoietin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF,

15 Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled

20 steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by

25 reference.

Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one anti-CNGH0010 antibody composition that total, on average, a range from at least about 0.01 to 500 milligrams of at least one anti-CNGH0010 antibody per kilogram of patient per dose, and, preferably, from at least about 0.1 to 100 milligrams antibody/kilogram of patient per

30 single or multiple administration, depending upon the specific activity of contained in the composition. Alternatively, the effective serum concentration can comprise 0.1-5000 µg/ml serum concentration per single or multiple administration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to

35 achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, i.e., repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

Preferred doses can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 mg/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 14.9, 15.0, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 µg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually, a dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.1 to 50, and preferably 0.1 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.1 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.

For parenteral administration, the antibody can be formulated as a solution, suspension, emulsion, particle, powder, or lyophilized powder in association, or separately provided, with a pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's

solution, dextrose solution, and 1-10% human serum albumin. Liposomes and nonaqueous vehicles, such as fixed oils, can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

- 5 Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Formulations

- As noted above, the invention provides for stable formulations, which preferably contain a
- 10 phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one anti-CNGH0010 antibody in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl
- 15 alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to, 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03,
- 20 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol (e.g., 0.2, 0.3, 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1, 1.5, 1.9, 2.0, 2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9,
- 25 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

- As noted above, the invention provides an article of manufacture, comprising packaging material and at least one vial comprising a solution of at least one anti-CNGH0010 antibody with the prescribed buffers and/or preservatives, optionally, in an aqueous diluent, wherein the packaging
- 30 material comprises a label that indicates that such solution can be held over a period of 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further comprises an article of manufacture, comprising packaging material, a first vial comprising lyophilized at least one anti-CNGH0010 antibody, and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein the packaging material comprises a label that instructs a patient to reconstitute
- 35 the at least one anti-CNGH0010 antibody in the aqueous diluent to form a solution that can be held over a period of twenty-four hours or greater.

The at least one anti-CNGH0010 antibody used in accordance with the present invention can be produced by recombinant means, including from mammalian cell or transgenic preparations, or can be purified from other biological sources, as described herein or as known in the art.

The range of at least one anti-CNGH0010 antibody in the product of the present invention
5 includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 μ g/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable
10 preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an anti-microbial effect. Such concentrations are dependent on the preservative
15 selected and are readily determined by the skilled artisan.

Other excipients, e.g., isotonicity agents, buffers, antioxidants, preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to
20 about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably the formulations of the present invention have pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably sodium phosphate, particularly phosphate buffered saline (PBS).

Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20
25 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants, such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyols, other block copolymers, and chelators such as EDTA and EGTA can optionally be added to the formulations or
30 compositions to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the protein to aggregate.

The formulations of the present invention can be prepared by a process which comprises mixing at least one anti-CNGH0010 antibody and a preservative selected from the group consisting of
35 phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one anti-CNGH0010

antibody and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one anti-CNGH0010 antibody in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the protein and preservative at the desired concentrations.

5 Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed formulations can be provided to patients as clear solutions or as dual vials
10 comprising a vial of lyophilized, at least one anti-CNGH0010 antibody that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably, a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

15 The present claimed articles of manufacture are useful for administration over a period of immediately to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the invention can optionally be safely stored at temperatures of from about 2 to about 40°C and retain the biological activity of the protein for extended periods of time, thus, allowing a package label indicating that the solution
20 can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to 1-12 months, one-half, one and a half, and/or two years.

The solutions of at least one anti-CNGH0010 antibody in the invention can be prepared by a process that comprises mixing at least one antibody in an aqueous diluent. Mixing is carried out using
25 conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one antibody in water or buffer is combined in quantities sufficient to provide the protein and, optionally, a preservative or buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the
30 formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed products can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized (at least one) anti-CNGH0010 antibody that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring
35 reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

The claimed products can be provided indirectly to patients by providing to pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized (at least one) anti-CNGH0010 antibody that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger in size, providing a large reservoir from which smaller portions of the at least one antibody solution can be retrieved one or multiple times for transfer into smaller vials and provided by the pharmacy or clinic to their customers and/or patients.

Recognized devices comprising these single vial systems include those pen-injector devices for delivery of a solution such as BD Pens, BD Autojector®, Humaject®, NovoPen®, B-D®Pen, AutoPen®, and OptiPen®, GenotropinPen®, GenotroNorm Pen®, Humatro Pen®, Reco-Pen®, Roferon Pen®, Biojector®, Iject®, J-tip Needle-Free Injector®, Intraject®, Medi-Ject®, e.g., as made or developed by Becton Dickinson (Franklin Lakes, NJ, www.bectondickenson.com), Disetronic (Burgdorf, Switzerland, www.disetronic.com; Bioject, Portland, Oregon (www.bioject.com); National Medical Products, Weston Medical (Peterborough, UK, www.weston-medical.com), Medi-Ject Corp (Minneapolis, MN, www.mediject.com). Recognized devices comprising a dual vial system include those pen-injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the reconstituted solution such as the HumatroPen®.

The products presently claimed include packaging material. The packaging material provides, in addition to the information required by the regulatory agencies, the conditions under which the product can be used. The packaging material of the present invention provides instructions to the patient to reconstitute the (at least one) anti-CNGH0010 antibody in the aqueous diluent to form a solution and to use the solution over a period of 2-24 hours or greater for the two vial, wet/dry, product. For the single vial, solution product, the label indicates that such solution can be used over a period of 2-24 hours or greater. The presently claimed products are useful for human pharmaceutical product use.

The formulations of the present invention can be prepared by a process that comprises mixing at least one anti-CNGH0010 antibody and a selected buffer, preferably, a phosphate buffer containing saline or a chosen salt. Mixing the (at least one) anti-CNGH0010 antibody and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one antibody in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the protein and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed stable or preserved formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized (at least one) anti-CNGH0010 antibody that is

reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

5 Other formulations or methods of stabilizing the anti-CNGH0010 antibody may result in other than a clear solution of lyophilized powder comprising the antibody. Among non-clear solutions are formulations comprising particulate suspensions, the particulates being a composition containing the anti-CNGH0010 antibody in a structure of variable dimension and known variously as a microsphere, microparticle, nanoparticle, nanosphere, or liposome. Such relatively homogenous essentially
10 spherical particulate formulations containing an active agent can be formed by contacting an aqueous phase containing the active and a polymer and a nonaqueous phase followed by evaporation of the nonaqueous phase to cause the coalescence of particles from the aqueous phase as taught in U.S. 4,589,330. Porous microparticles can be prepared using a first phase containing active and a polymer dispersed in a continuous solvent and removing the solvent from the suspension by freeze-drying or
15 dilution-extraction-precipitation as taught in U.S. Pat. 4,818,542. Preferred polymers for such preparations are natural or synthetic copolymers or polymer selected from the group consisting of glectin agar, starch, arabinogalactan, albumin, collagen, polyglycolic acid, polylactic acid, glycolide-L(-) lactide poly(epsilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), poly(epsilon-caprolactone-CO-glycolic acid), poly(beta-hydroxy butyric acid), polyethylene oxide, polyethylene,
20 poly(alkyl-2-cyanoacrylate), poly(hydroxyethyl methacrylate), polyamides, poly(amino acids), poly(2-hydroxyethyl DL-aspartamide), poly(ester urea), poly(L-phenylalanine/ethylene glycol/1,6-diisocyanatohexane) and poly(methyl methacrylate). Particularly preferred polymers are polyesters, such as polyglycolic acid, polylactic acid, glycolide-L(-) lactide poly(epsilon-caprolactone, poly(epsilon-caprolactone-CO-lactic acid), and poly(epsilon-caprolactone-CO-glycolic acid). Solvents
25 useful for dissolving the polymer and/or the active include: water, hexafluoroisopropanol, methylenechloride, tetrahydrofuran, hexane, benzene, or hexafluoroacetone sesquihydrate. The process of dispersing the active containing phase with a second phase may include pressure forcing the first phase through an orifice in a nozzle to effect droplet formation.

 Dry powder formulations may result from processes other than lyophilization, such as by
30 spray drying or solvent extraction by evaporation or by precipitation of a crystalline composition followed by one or more steps to remove aqueous or nonaqueous solvent. Preparation of a spray-dried antibody preparation is taught in U.S. Patent No. 6,019,968. The antibody-based dry powder compositions may be produced by spray drying solutions or slurries of the antibody and, optionally, excipients, in a solvent under conditions to provide a respirable dry powder. Solvents may include
35 polar compounds, such as water and ethanol, which may be readily dried. Antibody stability may be enhanced by performing the spray drying procedures in the absence of oxygen, such as under a nitrogen blanket or by using nitrogen as the drying gas. Another relatively dry formulation is a

dispersion of a plurality of perforated microstructures dispersed in a suspension medium that typically comprises a hydrofluoroalkane propellant as taught in WO 99/16419. The stabilized dispersions may be administered to the lung of a patient using a metered dose inhaler. Equipment useful in the commercial manufacture of spray dried medicaments are manufactured by Buchi Ltd. or Niro Corp.

5 At least one anti-CNGH0010 antibody in either the stable or preserved formulations or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means appreciated by the skilled artisan, as well-known in the art.

10

EXAMPLES OF INVENTION

 Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as
15 limiting.

 It will be clear that the invention can be practiced otherwise than as particularly described in the foregoing description and examples.

 Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

20

EXAMPLE 1

CNGH0010 Sequence Data

 The CNGH0010 genomic nucleotide sequence (SEQ ID NO:1) spans 16356 bp. Based on modeling with several gene prediction algorithms, such as GeneScan, Fgenesh (<http://genome.ucsc.edu/>) and the Acembly program (<http://www.acedb.org/Cornell/acembly/>),
25 CNGH0010 is predicted to comprise 25 exons (Fig. 1, Table 1). Exons 1, 7 and 18 each contain a start codon and are downstream from promoter, enhancer, and other regulatory motifs; these exons may be utilized as initiation exons. Exons 15 and 23 contain a stop codon and can be utilized as termination exons. Five categories of alternatively spliced transcripts have been identified and are exemplified in CNGH0010.1, CNGH0010.2, CNGH0010.3, CNGH0010.4, and CNGH0010.5 (SEQ
30 ID NOS: 2, 4, 6, 8, and 10, respectively, Table 2).

Table 1. CNGH0010 exon composition and description

Exon #	start position	stop position	# of bp	frame	Note
1	101	526	426	In	1 st ini. Exon; Constant for 10.1 and 10.2
2	786	986	201	In	Constant for 10.1 and 10.2
3	1099	1155	57	In	Constant for 10.1 and 10.2
4	1763	1813	51	In	Constant for 10.1 and 10.2
5	1983	2165	183	In	Constant for 10.1 and 10.2
5a	1983	2076	85	out	left exon
5b	2117	2165	91	out	right exon
6	2936	2980	45	In	rare exon
7	3149	3205	57	In	2 nd initiation exon; Constant for 10.3 and 10.4
7a	3168	3197	30	out	
8	3324	3392	69	In	Constant for 10.3 and 10.4
8a	3189	3392	204	out	overlap with exon 8 but longer
9	3615	3665	51	In	Alternatively spliced
10	5336	5371	36	In	Alternatively spliced
11	6065	6118	54	In	Alternatively spliced
12	7391	7450	60	In	Alternatively spliced
13	7590	7637	48	In	Constant for 10.1, 10.2, 10.3, and 10.4
14	7811	7858	48	In	Constant for 10.1, 10.2, 10.3, and 10.4
15	10129	10155	27	In	1 st term. Exon
16	10690	10746	57	In	Constant for 10.1, 10.2, 10.3, and 10.4
17	11393	11440	48	In	Constant for 10.1, 10.2, 10.3, and 10.4
18	11679	11753	75	In	3 rd initiation exon, constant for 10.5
19	12996	13043	48	In	Constant for 10.1, 10.3 and 10.5
20	13157	13198	42	In	Alternatively spliced
21	13547	13618	72	In	Constant for 10.1, 10.3 and 10.5
22	14679	14702	24	In	Constant for 10.1, 10.3 and 10.5
23	14813	14860	48	In	Constant for 10.1, 10.3 and 10.5
24	15895	15929	35	NA	3'UTR-1
25	16038	16356	319	NA	3'UTR-2

Table 2 shows the various CNGH0010 transcripts and exons contained within each transcript.

- 5 The exons shown in bold are constant in each transcript, while the other exons listed for each transcript are alternatively spliced and, optionally, part of various transcripts. As shown in Table 2, the nucleotide and amino acid sequences for each transcript vary depending on the exact combination of exons present.

Table 2. CNGH0010 transcripts description

<u>Transcript</u>	<u>Exons</u>	<u>Nucleotide Length (bp)</u>	<u>Peptide Length (aa)</u>
CNGH0010.1	<u>1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 20, 21, 22, 23, 24, 25</u>	1809/2132	459/555
CNGH0010.2	<u>1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 15</u>	1533/1734	373/440
CNGH0010.3	<u>7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 20, 21, 22, 23, 24, 25</u>	881/1159	172/253
CNGH0010.4	<u>7, 8, 9, 10, 11, 12, 13, 14, 15</u>	445/646	82/149
CNGH0010.5	<u>18, 19, 21, 22, 23, 25</u>	600	88

CNGH0010.1 is any transcript that starts with exon 1 and ends at exon 25, excluding exons 7, 15, and 18. It may have as few as 15 exons (i.e., exons 1-5, 8, 13, 14, 16, 17, 19, 21-23, and 25) or as many as 22 exons (i.e., exons 1-6, 8-14, 16, 17, and 19-25). Exons 6, 9-12, 20, and 24 can be differentially spliced, either individually or in any combination. Therefore, CNGH0010.1 transcripts range from 1809 to 2132 bp. They encode peptides ranging from 459 to 555 amino acids, depending on the exon composition.

CNGH0010.2 is any transcript that starts with exon 1 and ends at exon 15, excluding exons 6 and 7. It may have as few as 9 exons (i.e., exons 1-5, 8, and 13-15) or as many as 13 exons (i.e., exons 1-5 and 8-15). Exons 9-12 can be differentially spliced, either individually or in any combination. Therefore, CNGH0010.2 transcripts range from 1533 to 1734 bp, encoding peptides ranging from 373 to 440 amino acids, depending on the exon composition.

CNGH0010.3 is any transcript that starts with exon 7 and ends at exon 25, excluding exons 15 and 18. It may have as few as 11 exons (i.e., exons 7, 8, 13, 14, 16, 17, 19, 21-23, and 25) or as many as 17 exons (i.e., exons 7-14, 16, 17, and 19-25). Exons 9-12, 20, and 24 can be differentially spliced, either individually or in any combination. Therefore, CNGH0010.3 transcripts range from 881 to 1159 bp, encoding peptides ranging from 172 to 253 amino acids, depending on the exon composition.

CNGH0010.4 is any transcript that starts with exon 7 and ends at exon 15. It may have as few as 5 exons (i.e., exons 7, 8, and 13-15) or as many as 9 exons (i.e., exons 7-15). Exons 9-12 can be differentially spliced, either individually or in any combination. Therefore, CNGH0010.4 transcripts range from 445 to 646 bp, encoding peptides ranging from 82 to 149 amino acids, depending on the exon composition.

CNGH0010.5 is any transcript that starts with exon 18 and ends at exon 25, excluding exons 20 and 24. It has 6 exons, i.e., exons 18, 19, 21-23, and 25. The CNGH0010.5 transcript contains 600 bp encoding a peptide of 88 amino acids.

In addition to these 5 categories, a transcript that contains exons 5a, 5b, 7a, or 8a will have out-of-frame splicing at the site where these exons begin in the corresponding transcripts; this may

result in truncated proteins at the site of the exon or downstream of the exon. Often, the truncated proteins use an alternative initiation ATG codon in exon 13, at nucleotide position 7611.

The CNGH0010.1 amino acid sequence of SEQ ID NO:3 has 94% identity over 449 residues to GenBank Accession No. AY358412 (Pat. Publ. No. WO/200061623); the CNGH0010.2 amino acid sequence of SEQ ID NO:5 has 100% identity over 440 residues to Dgen No. AAF54238 (Pat. Publ. No. WO/200078961); the CNGH0010.3 amino acid sequence of SEQ ID NO:7 has 99% identity over 127 residues to Dgen No. AAH23810 (Pat. Publ. No. WO/200132888); the CNGH0010.4 amino acid sequence of SEQ ID NO:9 has 98% identity over 93 residues to Dgen No. ADE28278 (Pat. Publ. No. WO/2003046152); and the CNGH0010.5 amino acid sequence of SEQ ID NO:11 has 85% identity over 102 residues to Dgen No. AAF97894 (Pat. Publ. No. WO/200121658).

EXAMPLE 2

CNGH0010 Transcripts

5' and 3'-RACE (Rapid Analysis of cDNA Ends) was performed on total RNA from A431 cells and normal adult human male skin tissue according to the manufacturer's protocol (Catalog number L1502-01, Invitrogen, Corp., Carlsbad, CA). Briefly, 5 µg of total RNA was dephosphorylated with calf intestine alkaline phosphatase to remove phospho-groups from non-mRNA or truncated mRNA. The RNA was then treated with Tobacco Acid Pyrophosphatase to remove the 5' cap structure from mature mRNA. An RNA oligonucleotide of known sequence was then ligated to the 5' ends of mature mRNA, and then used as a template for reverse transcription with Superscript RT enzyme, primed with an oligo dT primer that also contained a unique known sequence. RT was carried out at 42 °C for 1.5 hours. The resulting cDNAs contained common sequences at their 5' ends and 3' ends, and could be used with nested oligonucleotides specific for the CNGH0010 gene (SEQ ID NOS:12-21, Table 3) to amplify all or part of the cDNA through PCR.

Table 3. RACE primers

<u>SEQ ID NO:</u>	<u>Oligo name</u>	<u>Sequence and exon</u>
12	CNGH0010EX1F	GGC TGG GCA GAG ATG AAG TTC CAG EXON1
13	CNGH0010EX1FNEST	TCT GCC TGG GCA GTG GGG AG EXON1
14	CNGH0010EX7F	ATG CTC GGA ATA ACT TCC TGC AGC G EXON7
15	CNGH0010EX7FNEST	GCA GCG ACC AAC AGG CTA AAG EXON7
16	CNGH0010EX18F	ATG AAG CCG GCC ACT GCC TCTG EXON18
17	CNGH0010EX18FNEST	CTC TGC TCC TGC TCC TGC TG EXON18
18	CNGH0010UTR2R	GGG CCA GGG CTG GCA CAG GC UTR2
19	CNGH0010UTR2NEST	CGG GGC CTC GGT GGT GGT TGC UTR2
20	CNGH0010EX15R	TCT GGT GGC TCC TTG TCT GGA GGT C EXON15
21	CNGH0010EX15RNEST	GTC ACG GGA TGC GAG AGC TTC TCT GGT C EXON15

SEQ ID NOS:12 or 13 in exon 1 with SEQ ID NOS:18 or 19 in exon 25 (3'UTR-2) were used to amplify CNGH0010.1 transcripts. SEQ ID NOS:12 or 13 with SEQ ID NOS:20 or 21 in exon 15 were used to amplify CNGH0010.2 transcripts. SEQ ID NOS:14 or 15 in exon 7 with SEQ ID NOS:18 or 19 in exon 25 were used to amplify CNGH0010.3 transcripts. SEQ ID NOS:14 or 15 in exon 7 with SEQ ID NOS:20 or 21 in exon 15 were used to amplify CNGH0010.4 transcripts. SEQ ID NOS:16 or 17 in exon 18 with SEQ ID NOS:18 or 19 in exon 25 were used to amplify CNGH0010.5 transcripts. RT-PCR data, as shown in Fig. 2, demonstrated that the transcripts of CNGH0010.1 (SEQ ID NO:2), 10.2 (SEQ ID NO:4) are at the highest level, followed by 10.5 (SEQ ID NO:10) at a lower level, 10.4 (SEQ ID NO:8) at a significantly lower level, and 10.3 (SEQ ID NO:6) at the lowest level of all of the transcripts.

As shown in Table 4 below, five sets of forward/reverse primers and probes were designed to identify the five dominant splice variants by real time PCR application. For each splice variant, the forward and reverse primers and Taqman probe are shown. Total RNA extracted from A431 and HCT116 cells treated with various concentrations of TNF α , LPS, and IL-12 was reversed transcribed into a cDNA template, which was then amplified by real time PCR using these 5 sets of primers/probes. CNGH0010.2 and CNGH0010.5 were upregulated by various concentrations of TNF α , LPS, and IL-12.

Table 4. Forward/reverse primers and probes of real time PCR for splice variants

Splice variant	Forward primer	Reverse primer	Taqman Probe
CNGH0010.1	SEQ ID NO:25: GAGGTGACAGCG GCAGTGAGT	SEQ ID NO:26: TTAAATTCCTCCAGA AAGTGTC AAAGTTA	SEQ ID NO:27: ATTCAGAACTCTGA GACGTC
CNGH0010.2	SEQ ID NO:28: TGTTGGTGGAGTC AATACTGTGAACT	SEQ ID NO:29: CGGGATGCGAGAGCTT CTC	SEQ ID NO:30: CACTTTCTGGAAGA ATTTTAAATC
CNGH0010.3	SEQ ID NO:31: GGAGCGGCGGAG GAAAT	SEQ ID NO:32: TGATGAAACCCAGCTT GGATT	SEQ ID NO:33: AAACCCGGAACCT CTGAGAC
CNGH0010.4	SEQ ID NO:34: GGCGGAGGAAAT GGACATAAA	SEQ ID NO:35: GAGCTTCTCTGGTCCTT GTTTATGG	SEQ ID NO:36: AATCTGGGATTTCAG AACTC
CNGH0010.5	SEQ ID NO:37: GGGTGCGGACGC GTCAT	SEQ ID NO:38: GTCTTGACTGAGTACT TCCCACCATAG	SEQ ID NO:39: ACGATCAGAACTA CAATTACAAC

EXAMPLE 3

Predicted CNGH0010 Protein Domains

The CNGH0010.1 and CNGH0010.2 polypeptides may contain up to 555 and 440 amino acids, respectively (SEQ ID NOS:3 and 5, respectively). The first 21 amino acids encode a signal peptide, followed by five major domains (Fig. 3). The first domain, which includes the signal peptide, is encoded by exon 1, and has no significant homology to any known proteins or protein domains. This domain is predicted to form at least 6 subdomains of alpha-helical secondary structure based on the NNPredict program. The second domain, encoded by exon 2, possesses 19 Glycine-X-Y repeats that are known to form coiled-coiled structures, as seen in collagen and collagen-like molecules. This domain is then followed by a differentially spliced serine-glycine rich domain (up to 42% serine, 37% glycine), encoded by exons 4-8. The differential splicing appears to alter the size and amount of serine-glycine residues.

A differentially spliced spacer domain is encoded by exons 9-17. The exons encoding this region are very small, ranging in size from 36 to 60 nucleotides. This region is predicted to have minimal if any secondary structure using the NNPredict program. The differential splicing that occurs in this region appears to regulate the distance between the serine-glycine rich domain, and the C-terminal domain. The CNGH0010.1 (SEQ ID NO:3) terminates in another domain encoded by exons 19-23 that has no homology to any known proteins. This domain is predicted to have at least 2 regions of predicted alpha-helix. The CNGH0010.2 (SEQ ID NO:5) polypeptide possesses all of the domains included in the 10.1 (SEQ ID NO:3) polypeptide, except for the C-terminal domain encoded by exons 19-23. The CNGH0010.3 (SEQ ID NO:7) polypeptide may contain up to 253 amino acids and contains part of the differentially spliced Serine-Glycine rich domain, the differentially spliced spacer domain, and the C-terminal domain. The CNGH0010.4 (SEQ ID NO:9) polypeptide may contain up to 149 and includes part of the differentially spliced Serine-Glycine rich domain and the differentially spliced spacer domain. Finally, the CNGH0010.5 (SEQ ID NO:11) polypeptide has 88 amino acids and contains essentially the C-terminal domain, preceded by a signal peptide encoded by exon 18.

The domains of CNGH0010 allow for the assembly of a homo (all CNGH0010.1 (SEQ ID NO:3)) or all CNGH0010.2 (SEQ ID NO:5)) or hetero (mixture of CNGH0010.1 (SEQ ID NO:3) and CNGH0010.2 (SEQ ID NO:5))-trimers, such as collagens or adiponectin, through the collagen-like coiled-coil region. The presence of proline residues at some of the X-Y positions of the Gly-X-Y repeat is thought to stabilize these trimers, by unknown mechanisms and thus provides further evidence that the molecule might form collagen-like structures. Preliminary biochemical characterization of recombinantly expressed CNGH0010.2 (SEQ ID NO:5) polypeptide indicates that this molecule does indeed form oligomers. SDS-PAGE analysis (as shown in Fig. 4) indicates that molecules with molecular weights of 2, 3 and 4 times that of the single chain exist in both non-

reduced and reduced samples, indicating that some of the oligomers are covalently bound. This result has been confirmed by SELDI mass spectrometry and gel filtration HPLC. As seen in collagen molecules, covalent cross-linking between trimer chains can be seen by post-translational modification of Lysine residues present in the polypeptide. This modification results in covalent dimer, trimer, and multimers (fibrils) of the polypeptide. The CNGH0010.5 (SEQ ID NO:11) molecules are essentially the C-terminal domain and may have unique functional activity.

EXAMPLE 4

Secretion of CNGH0010 Polypeptides

The CNGH0010.1 and 10.2 polypeptides contain the same predicted signal sequence (amino acids 1-21 in SEQ ID NOS:3 and 5). The predicted CNGH0010.5 polypeptide sequence has a different signal sequence (amino acids 1-24 in SEQ ID NO:11). *In vitro* transient expression of a His tagged CNGH0010.2 fusion protein, as well as a CNGH0010.5 mimetibody (the details of which are described in Example 6), confirmed that the signal sequences indeed target these polypeptides for extracellular secretion. Therefore, CNGH0010.1 (SEQ ID NO:3), 10.2 (SEQ ID NO:5), and 10.5 (SEQ ID NO:11) polypeptides probably are secreted into the extracellular space where they might exert their effects. CNGH0010.3 and CNGH0010.4 (SEQ ID NOS:7 and 9) do not contain a signal sequence.

EXAMPLE 5

Relative CNGH0010 Transcript Levels in Selected Disease Tissues

CNGH0010 primers and probes, Primers: CNGH00010ss1 - GGC GGA GGA AAT GGA CAT AA (SEQ ID NO:23), CNGH00010as1 - GCT TGG ATT TAA AAT TCT TCC AGA AA (SEQ ID NO:24), TaqMan MGB Probe: CNGH00010p1 - 6FAM - GCT TTT CAC ACC CGG GT - MGBNFQ (SEQ ID NO:22) were designed using Primer Express software and synthesized by Applied Biosystem (Foster City, CA). Total RNAs were isolated from different tissues, reverse transcribed and amplified by PCR using these primers/probes. Relative transcript levels of CNGH0010 are shown below in Table 5.

Table 5. Distribution of CNGH0010 in different human disease tissues

Tissues	Disease	Fold change*
Brain	Normal	1.00
Lung	Emphysema	4.58
Lung	respiratory infection	0.19
Tonsil	Tonsillitis	1.63
Thyroid	grave's disease	8.35
Thyroid	lymphocytic thyroidities	3.90
Pancreas	Diabetes	9.45
Pancreas	Pancreatitis	0.86
Liver	Cirrhosis	0.45
Colon	Colitis	0.24

Tissues	Disease	Fold change*
Colon	UC	0.22
Synovium	osteoarthritis/DJD	0.14
Catilage	osteoarthritis/DJD	1.32
Ovary	endometriosis	2.18
Bladder	cystitis	0.19
Lymphoma	hodgkin	0.06
Sarcoma		0.21

* The level of CNGH0010 in each tissue is compared to the level in normal brain tissue that acts as the control (1.00 Fold Change).

When compared with calibration tissue, normal human brain RNA, an increase in CNGH0010 mRNA level was detected in emphysematous lung tissue, thyroid tissue from Grave's disease patient or inflammatory thyroiditis, inflamed tonsil, ovary from endometriosis patient, diabetic pancreas and osteoarthritic cartilage.

EXAMPLE 6

Protein Expression

Expression of the CNGH0010.2 (SEQ ID NO:5) protein was performed by cloning most of a CNGH0010.2 transcript containing exons 1-5, 8, 9, 12 and part of 13 inframe of a hexa-His tag in an expression vector driven by a CMV promoter. This construct was transfected into HEK293 cells and purified with the His tag. The N-terminal sequence of the expressed and purified material confirmed the identity of the purified protein and demonstrated signal peptide cleavage. SDS-PAGE analysis of the expressed and purified protein indicated that the molecule forms oligomers (Fig. 4), which was confirmed by non-reducing MS-SELDI (surface enhanced laser desorption/ionization) and gel filtration HPLC. This data indicates that the CNGH0010.2 and CNGH0010.1 transcripts, since they contain the same signal sequence encoded by exon 1, have the ability to be secreted extracellularly. In addition, the SDS-PAGE, SELDI-MS, and gel filtration HPLC indicate that this molecule has the ability to form oligomers.

CNGH0010.5 (SEQ ID NO:11) could not be expressed alone in HEK293 cells; however, it was engineered as a mimetibody. Most of the CNGH0010.5 coding region containing amino acids 1 to 86 were engineered into an expression plasmid that contained the the human IgH J2 segment fused to the human IgG1 hinge, CH₂ and CH₃. The plasmid contained a CMV promoter for transcription of recombinant genes, and utilized the CNGH0010.5 endogenous signal sequence encoding amino acids 1-24. This construct was transiently transfected into HEK293 cells, and the resulting secreted molecules purified by protein A affinity beads. SDS-PAGE analysis confirmed that a protein of predicted molecular weight containing the CNGH0010.5 mature amino acid sequence, followed by the J2, hinge, CH₂ and CH₃ of the human IgG1 had been expressed.

The expression levels of the CNGH0010.2 (SEQ ID NO:5) and CNGH0010.5 (SEQ ID NO:11) proteins in A431 and HCT116 cells were measured in response to stimulation by TNF- α and LPS. Stimulation by TNF- α and LPS caused an increase in CNGH0010.2 (SEQ ID NO:5) and CNGH0010.5 (SEQ ID NO:11) expression. Similarly, expression of CNGH0010.2 (SEQ ID NO:5) and CNGH0010.5 (SEQ ID NO:11) was increased in the presence of IL-12. Additionally, IL-6, IL-8, and GMCSF levels were increased by TNF- α treatment in A431 cells and they were reduced in the presence of a chimeric, anti-TNF- α antibody. IL-6 is an important inflammatory cytokine, the increase of this cytokine accompanied by the increase of CNGH0010.2 and 10.5 with TNF- α treatment indicates a possible mechanism of CNGH0010 and inflammatory responses. IL-8 is a chemokine that plays a critical role in inflammation. It recruits lymphocytes and leukocytes to the inflammatory site and stimulates other cytokine production. GMCSF is a stimulator for macrophage/monocytes as well as other lymphocytes, which also play roles in the inflammatory responses. This evidence suggests that CNGH0010 may play a role in the inflammatory regulation, therefore it could be a good target for therapeutic development.

Although illustrated and described above with reference to certain specific embodiments, the present invention is nevertheless not intended to be limited to the details shown. Rather, the present invention is directed to the CNGH0010 polypeptides, polynucleotides, antibodies, apparatus, and kits disclosed herein and uses thereof, and various modifications may be made in the details within the scope and range of equivalents of the claims and without departing from the spirit of the invention.

20

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. An isolated nucleic acid molecule comprising the nucleotide sequence SEQ ID NO: 2, or an exact complement of said nucleotide sequence.
- 5 2. An isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having the amino acid sequence SEQ ID NO: 3.
3. An isolated nucleic acid molecule encoding a naturally occurring allelic variant of a polypeptide having the amino acid sequence SEQ ID NO: 3.
4. An isolated nucleic acid molecule comprising a nucleotide sequence having at
10 least 90% identity to SEQ ID NO: 2, or an exact complement of said nucleotide sequence.
5. An isolated nucleic acid molecule comprising a nucleotide sequence having at least 70% identity to SEQ ID NO: 2, or an exact complement of said nucleotide sequence.
- 15 6. An isolated polypeptide comprising the amino acid sequence SEQ ID NO: 3.
7. An isolated polypeptide comprising an amino acid sequence having at least 90% identity to the amino acid sequence SEQ ID NO: 3.
8. A fusion polypeptide comprising the polypeptide of claim 6 or claim 7 operably linked to a heterologous polypeptide.
- 20 9. The fusion polypeptide of claim 8 wherein the heterologous polypeptide is a member of the immunoglobulin protein family or a fragment of said member.
10. The polypeptide of any one of claims 6 to 9, wherein said polypeptide has at least one activity of a CNGH0010 polypeptide.
11. An isolated antibody comprising a monoclonal or polyclonal antibody that
25 specifically binds to a polypeptide of any one of claims 6 to 10.
12. An isolated nucleic acid molecule encoding the antibody of claim 11.

13. A vector comprising the nucleic acid molecule of any one of claims 1 to 5 or 12.
14. A host cell containing the nucleic acid molecule of any one of claims 1 to 5 or 12.
15. A method for producing an isolated antibody, comprising translating the nucleic acid molecule of claim 12, under conditions *in vitro*, *in vivo* or *in situ*, wherein the antibody is expressed in detectable or recoverable amounts.
16. An isolated antibody produced by the method of claim 15.
17. A method for producing an isolated polypeptide, comprising translating the nucleic acid molecule of any one of claims 1 to 5, under conditions *in vitro*, *in vivo* or *in situ*, wherein the polypeptide is expressed in detectable or recoverable amounts.
18. An isolated polypeptide produced by the method of claim 17.
19. A composition comprising one or more of:
- a) the nucleic acid molecule of any one of claims 1 to 5 or 12,
 - b) the polypeptide of any one of claims 6 to 10 or 18, or
 - c) the antibody of claim 11 or claim 16.
20. A method of diagnosing a CNGH0010-related condition in a subject, comprising detecting one or more of:
- a) the nucleic acid molecule of any one of claims 1 to 5 or 12,
 - b) the polypeptide of any one of claims 6 to 10 or 18, or
 - c) the antibody of claim 11 or claim 16.
21. A method of treating a CNGH0010-related condition in a subject, comprising administering to the subject the composition of claim 19.
22. Use of the composition of claim 19 for the preparation of a medicament for treating a CNGH0010-related condition.
23. A method of treating an epithelial-related condition in a subject, comprising administering to the subject the composition of claim 19.
24. Use the composition of claim 19 for the preparation of a medicament for treating an epithelial-related condition.

2004237766 28 Jul 2010

- 58 -

25. An article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising one or more of:

- a) the nucleic acid molecule of any one of claims 1 to 5 or 12,
- b) the polypeptide of any one of claims 6 to 10 or 18, or
- 5 c) the antibody of claim 11 or claim 16.

26. The article of manufacture of claim 25, wherein said container is a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic,
10 intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

27. An isolated nucleic acid molecule according to any one of claims 1 to 5 or 12; an
15 isolated polypeptide according to any one of claims 6, 7 or 18; a fusion polypeptide according to claim 8; an isolated antibody according to claim 11 or claim 16; a vector according to claim 13; a host cell according to claim 14; a method according to any one of claims 15, 17, 20, 21 or 23; a composition according to claim 19; use according to claim 22 or claim 24; or an article of manufacture according to claim 25, substantially as
20 herein described with reference to any one or more of the examples but excluding comparative examples.

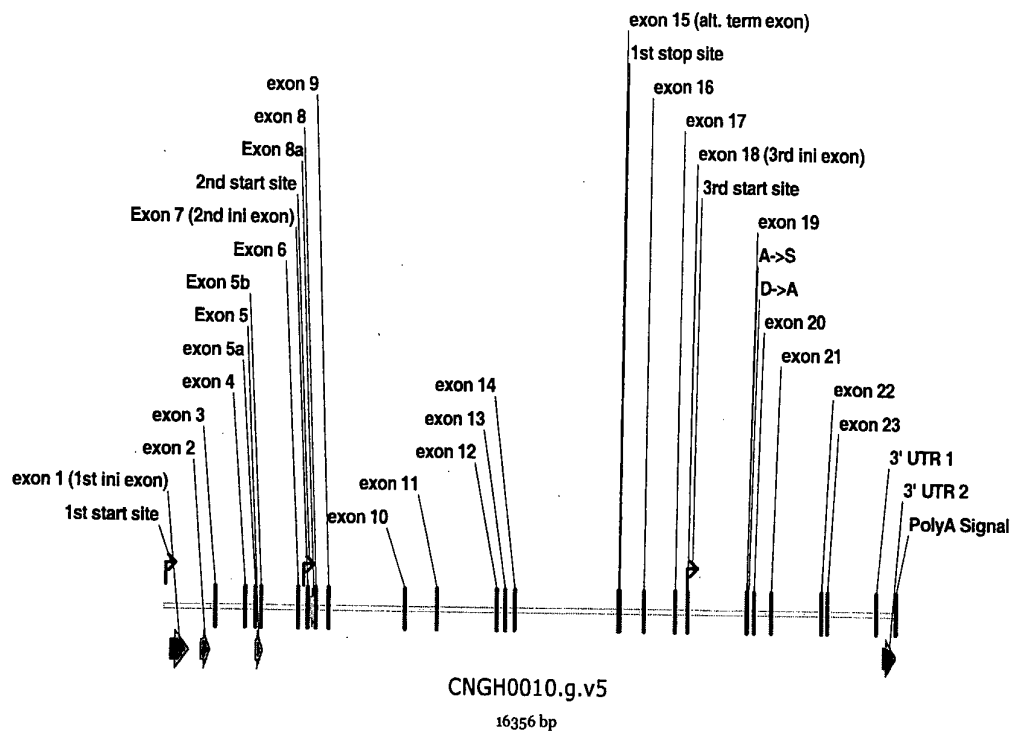


Figure 1

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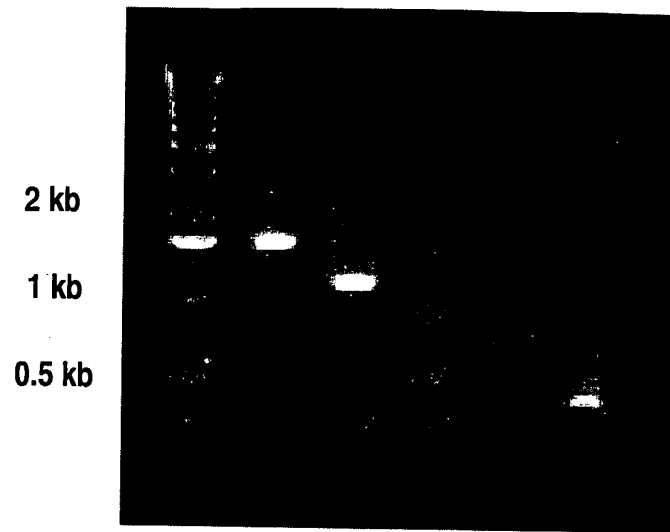


Figure 2

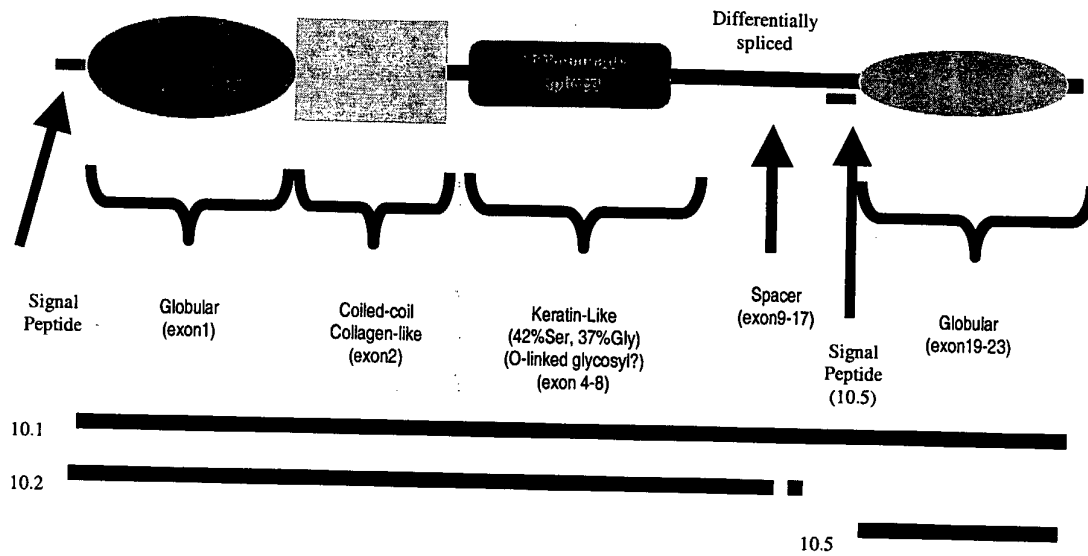


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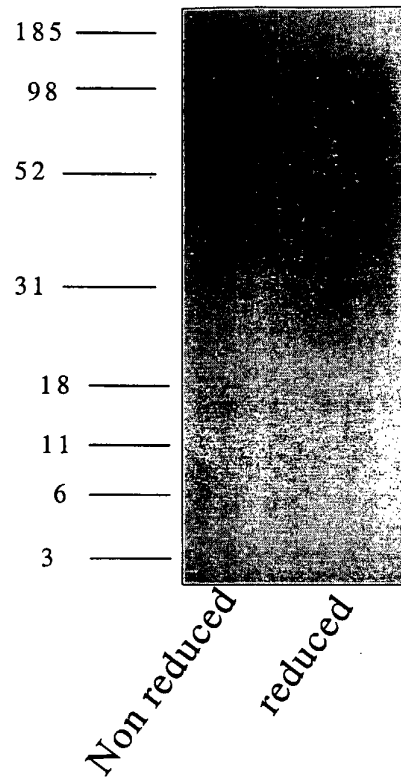


Figure 4

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Ma, Keying
Liang, Bailin
Naso, Michael

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COMPOSITIONS, METHODS AND USES

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Page 3

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gcc ctc ctc tac ttc agc cga ctc tgg gag gtaggagaat tcttgctgtt 10766
Ala Leu Leu Tyr Phe Ser Arg Leu Trp Glu
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CNGH0010_sequence_listing.txt

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		Asp	Phe Lys Gln Asn Thr Pro Phe Leu			
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Asn Trp Lys Ala Ile Ile Glu						
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			Met Lys Pro Ala Thr Ala Ser Ala			
				510		
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Trp						
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CNGH0010_sequence_listing.txt

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Gly Ala Gly Trp Gln Glu Val Ala Ala Val Thr Ser Lys
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                                Asn Tyr Asn Tyr Asn Gln
                                565

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His Ala Tyr Pro Thr Ala Tyr Gly Gly Lys Tyr Ser Val Lys Thr Pro
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Ala Lys

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CNGH0010_sequence_listing.txt

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Val Ser Pro Ser Ser Ser	590
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	Ala Ser Arg Val Gln Pro Gly Leu Leu Gln Trp 595 600
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Val Lys Phe Trp	605
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Page 14

CNGH0010_sequence_listing.txt

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gca gcc cat gct ctg gga aac act ggg cac gag att ggc aga cag gca Ala Ala His Ala Leu Gly Asn Thr Gly His Glu Ile Gly Arg Gln Ala 105 110 115	451
gaa gat gtc att cga cac gga gca gat gct gtc cgc ggc tcc tgg cag Glu Asp Val Ile Arg His Gly Ala Asp Ala Val Arg Gly Ser Trp Gln 120 125 130	499
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cag cct ggc tat ggt tca gtg aga gcc agc aac cag aat gaa ggg tgc Gln Pro Gly Tyr Gly Ser Val Arg Ala Ser Asn Gln Asn Glu Gly Cys 215 220 225	787
acg aat ccc cca cca tct ggc tca ggt gga ggc tcc agc aac tct ggg Thr Asn Pro Pro Pro Ser Gly Ser Gly Gly Ser Ser Asn Ser Gly 230 235 240 245	835
gga ggc agc ggc tca cag tcg ggc agc agt ggc agt ggc agc aat ggt Gly Gly Ser Gly Ser Gln Ser Gly Ser Ser Gly Ser Gly Ser Asn Gly 250 255 260	883
gac aac aac aat ggc agc agc agt ggt ggc agc agc agt ggc agc agc Asp Asn Asn Asn Gly Ser Ser Ser Gly Gly Ser Ser Ser Gly Ser Ser 265 270 275	931
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CNGH0010_sequence_listing.txt

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Lys Pro Gly Cys Glu Lys Pro Gly Asn Glu Ala Arg Gly Ser Gly Glu	
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tct ggg att cag ggc ttc aga gga cag gga gtt tcc agc aac atg agg	1219
Ser Gly Ile Gln Gly Phe Arg Gly Gln Gly Val Ser Ser Asn Met Arg	
360 365 370	
gaa ata agc aaa gag ggc aat cgc ctc ctt gga ggc tct gga gac aat	1267
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Tyr Arg Gly Gln Gly Ser Ser Trp Gly Ser Gly Gly Gly Asp Ala Val	
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ggt gga gtc aat att cag aac tct gag acg tct cct ggg atg ttt aac	1363
Gly Gly Val Asn Ile Gln Asn Ser Glu Thr Ser Pro Gly Met Phe Asn	
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Phe Asp Thr Phe Trp Lys Asn Phe Lys Ser Lys Leu Gly Phe Ile Asn	
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Leu Leu Tyr Phe Ser Arg Leu Trp Glu Asp Phe Lys Gln Asn Thr Pro	
455 460 465	
ttc ctc aac tgg aaa gca att att gag ggt gcg gac gcg tca tca ctg	1555
Phe Leu Asn Trp Lys Ala Ile Ile Glu Gly Ala Asp Ala Ser Ser Leu	
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cag aaa cgt gca ggc aga gcc gat cag ccg ggt gca gga tgg cag gag	1603
Gln Lys Arg Ala Gly Arg Ala Asp Gln Pro Gly Ala Gly Trp Gln Glu	
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Val Ala Ala Val Thr Ser Lys Asn Tyr Asn Tyr Asn Gln His Ala Tyr	
505 510 515	
ccc act gcc tat ggt ggg aag tac tca gtc aag acc cct gca aag ggg	1699
Pro Thr Ala Tyr Gly Gly Lys Tyr Ser Val Lys Thr Pro Ala Lys Gly	
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gga gtc tca cct tct tcc tcg gct tcc cgg gtg caa cct ggc ctg ctg	1747
Gly Val Ser Pro Ser Ser Ser Ala Ser Arg Val Gln Pro Gly Leu Leu	
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Gln Trp Val Lys Phe Trp	
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CNGH0010_sequence_listing.txt

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Glu Gly Val Gly Lys Ala Ile Gly Lys Glu Ala Gly Gly Ala Ala Gly
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Ser Lys Val Ser Glu Ala Leu Gly Gln Gly Thr Arg Glu Ala Val Gly
 65 70 75 80

Thr Gly Val Arg Gln Val Pro Gly Phe Gly Ala Ala Asp Ala Leu Gly
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Asn Arg Val Gly Glu Ala Ala His Ala Leu Gly Asn Thr Gly His Glu
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Ile Gly Arg Gln Ala Glu Asp Val Ile Arg His Gly Ala Asp Ala Val
 115 120 125

Arg Gly Ser Trp Gln Gly Val Pro Gly His Asn Gly Ala Trp Glu Thr
 130 135 140

Ser Gly Gly His Gly Ile Phe Gly Ser Gln Gly Gly Leu Gly Gly Gln
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Gly Gln Gly Asn Pro Gly Gly Leu Gly Thr Pro Trp Val His Gly Tyr
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Pro Gly Asn Ser Ala Gly Ser Phe Gly Met Asn Pro Gln Gly Ala Pro
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CNGH0010_sequence_listing.txt

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 225 230 235 240
 Ser Ser Asn Ser Gly Gly Gly Ser Gly Ser Gln Ser Gly Ser Ser Gly
 245 250 255
 Ser Gly Ser Asn Gly Asp Asn Asn Asn Gly Ser Ser Ser Gly Gly Ser
 260 265 270
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 Gln Gly Ser Ser Thr Gly Ser Ser Ser Gly Asn His Gly Gly Ser Gly
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 Arg Gly Ser Gly Glu Ser Gly Ile Gln Gly Phe Arg Gly Gln Gly Val
 355 360 365
 Ser Ser Asn Met Arg Glu Ile Ser Lys Glu Gly Asn Arg Leu Leu Gly
 370 375 380
 Gly Ser Gly Asp Asn Tyr Arg Gly Gln Gly Ser Ser Trp Gly Ser Gly
 385 390 395 400
 Gly Gly Asp Ala Val Gly Gly Val Asn Ile Gln Asn Ser Glu Thr Ser
 405 410 415
 Pro Gly Met Phe Asn Phe Asp Thr Phe Trp Lys Asn Phe Lys Ser Lys
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 Leu Gly Phe Ile Asn Trp Asp Ala Ile Asn Lys Asn Gln Val Pro Pro
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CNGH0010_sequence_listing.txt

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 485 490 495

Ala Gly Trp Gln Glu Val Ala Ala Val Thr Ser Lys Asn Tyr Asn Tyr
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 <213> Homo sapiens

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 ggcggcaagg aggagaccct ggtgggagga agacactctg gagagagagg gggctgggca 180
 gag atg aag ttc cag ggg ccc ctg gcc tgc ctc ctg ctg gcc ctc tgc 228
 Met Lys Phe Gln Gly Pro Leu Ala Cys Leu Leu Leu Ala Leu Cys
 1 5 10 15
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 Leu Gly Ser Gly Glu Ala Gly Pro Leu Gln Ser Gly Glu Glu Ser Thr
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 Gly Thr Asn Ile Gly Glu Ala Leu Gly His Gly Leu Gly Asp Ala Leu
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 Ser Glu Gly Val Gly Lys Ala Ile Gly Lys Glu Ala Gly Gly Ala Ala
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CNGH0010_sequence_listing.txt

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ccc tgg ggt caa gga ggc aat gga ggg cca cca aac ttt ggg acc aac Pro Trp Gly Gln Gly Gly Asn Gly Gly Pro Pro Asn Phe Gly Thr Asn 205	804
act cag gga gct gtg gcc cag cct ggc tat ggt tca gtg aga gcc agc Thr Gln Gly Ala Val Ala Gln Pro Gly Tyr Gly Ser Val Arg Ala Ser 220	852
aac cag aat gaa ggg tgc acg aat ccc cca cca tct ggc tca ggt gga Asn Gln Asn Glu Gly Cys Thr 230 Asn Pro Pro Ser 235 Gly Ser Gly Gly 235	900
ggc tcc agc aac tct ggg gga ggc agc ggc tca cag tcg ggc agc agt Gly Ser Ser Asn Ser Gly Gly Gly Ser Gly Ser 250 Gln Ser Gly Ser Ser 255	948
ggc agt ggc agc aat ggt gac aac aac aat ggc agc agc agt ggt ggc Gly Ser Gly Ser Asn Gly Asp Asn Asn Asn Gly Ser Ser Ser Gly Gly 270	996
agc agc agt ggc agc agc agt ggc agc agc agt ggc ggc agc agt ggc Ser Ser Ser Gly Ser Ser Ser Gly Ser Ser Ser Gly Gly Ser Ser Gly 285	1044
ggc agc agt ggt ggc agc agt ggc aac agt ggt ggc agc aga ggt gac Gly Ser Ser Gly Gly Ser Ser Ser Gly Asn Ser Gly Gly Ser Arg Gly Asp 300	1092
agc ggc agt gag tcc tcc tgg gga tcc agc acc ggc tcc tcc tcc ggc Ser Gly Ser Ser Glu Ser Ser Trp 310 Gly Ser Ser Thr 315 Ser Ser Ser Ser Gly 315	1140

CNGH0010_sequence_listing.txt

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aac cac ggt ggg agc ggc gga gga aat gga cat aaa ccc ggg tgt gaa 1188
Asn His Gly Gly Ser Gly Gly Gly Asn Gly His Lys Pro Gly Cys Glu
320 325 330 335

aag cca ggg aat gaa gcc cgc ggg agc ggg gaa tct ggg att cag ggc 1236
Lys Pro Gly Asn Glu Ala Arg Gly Ser Gly Glu Ser Gly Ile Gln Gly
340 345 350

ttc aga gga cag gga gtt tcc agc aac atg agg gaa ata agc aaa gag 1284
Phe Arg Gly Gln Gly Val Ser Ser Asn Met Arg Glu Ile Ser Lys Glu
355 360 365

ggc aat cgc ctc ctt gga ggc tct gga gac aat tat cgg ggg caa ggg 1332
Gly Asn Arg Leu Leu Gly Gly Ser Gly Asp Asn Tyr Arg Gly Gln Gly
370 375 380

tcg agc tgg ggc agt gga gga ggt gac gct gtt ggt gga gtc aat act 1380
Ser Ser Trp Gly Ser Gly Gly Gly Asp Ala Val Gly Gly Val Asn Thr
385 390 395

gtg aac tct gag acg tct cct ggg atg ttt aac ttt gac act ttc tgg 1428
Val Asn Ser Glu Thr Ser Pro Gly Met Phe Asn Phe Asp Thr Phe Trp
400 405 410 415

aag aat ttt aaa tcc aag ctg ggt ttc atc aac tgg gat gcc ata aac 1476
Lys Asn Phe Lys Ser Lys Leu Gly Phe Ile Asn Trp Asp Ala Ile Asn
420 425 430

aag gac cag aga agc tct cgc atc ccg tga cctccagaca aggagccacc 1526
Lys Asp Gln Arg Ser Ser Arg Ile Pro
435 440

agattggatg ggagccccc cactccctcc ttaaaacacc accctctcat cactaatctc 1586

agcccttgcc cttgaaataa accttagctg ccccaaaaaa aaaaaaaaaa aaaaaaaaaa 1646

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1706

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1734

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<210> 5
<211> 440
<212> PRT
<213> Homo sapiens

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<400> 5
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Met Lys Phe Gln Gly Pro Leu Ala Cys Leu Leu Leu Ala Leu Cys Leu
1 5 10 15
```

```
Gly Ser Gly Glu Ala Gly Pro Leu Gln Ser Gly Glu Glu Ser Thr Gly
20 25 30
```

```
Thr Asn Ile Gly Glu Ala Leu Gly His Gly Leu Gly Asp Ala Leu Ser
35 40 45
```

```
Glu Gly Val Gly Lys Ala Ile Gly Lys Glu Ala Gly Gly Ala Ala Gly
50 55 60
```

CNGH0010_sequence_listing.txt

Ser Lys Val Ser Glu Ala Leu Gly Gln Gly Thr Arg Glu Ala Val Gly
 65 70 75 80
 Thr Gly Val Arg Gln Val Pro Gly Phe Gly Ala Ala Asp Ala Leu Gly
 85 90 95
 Asn Arg Val Gly Glu Ala Ala His Ala Leu Gly Asn Thr Gly His Glu
 100 105 110
 Ile Gly Arg Gln Ala Glu Asp Val Ile Arg His Gly Ala Asp Ala Val
 115 120 125
 Arg Gly Ser Trp Gln Gly Val Pro Gly His Ser Gly Ala Trp Glu Thr
 130 135 140
 Ser Gly Gly His Gly Ile Phe Gly Ser Gln Gly Gly Leu Gly Gly Gln
 145 150 155 160
 Gly Gln Gly Asn Pro Gly Gly Leu Gly Thr Pro Trp Val His Gly Tyr
 165 170 175
 Pro Gly Asn Ser Ala Gly Ser Phe Gly Met Asn Pro Gln Gly Ala Pro
 180 185 190
 Trp Gly Gln Gly Gly Asn Gly Gly Pro Pro Asn Phe Gly Thr Asn Thr
 195 200 205
 Gln Gly Ala Val Ala Gln Pro Gly Tyr Gly Ser Val Arg Ala Ser Asn
 210 215 220
 Gln Asn Glu Gly Cys Thr Asn Pro Pro Pro Ser Gly Ser Gly Gly Gly
 225 230 235 240
 Ser Ser Asn Ser Gly Gly Gly Ser Gly Ser Gln Ser Gly Ser Ser Gly
 245 250 255
 Ser Gly Ser Asn Gly Asp Asn Asn Asn Gly Ser Ser Ser Gly Gly Ser
 260 265 270
 Ser Ser Gly Ser Ser Ser Gly Ser Ser Ser Gly Gly Ser Ser Gly Gly
 275 280 285
 Ser Ser Gly Gly Ser Ser Gly Asn Ser Gly Gly Ser Arg Gly Asp Ser
 290 295 300
 Gly Ser Glu Ser Ser Trp Gly Ser Ser Thr Gly Ser Ser Ser Gly Asn

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<210> 6
<211> 1124
<212> DNA
<213> Homo sapiens
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<220>
<221> CDS
<222> (44)..(805)
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[illegible]

CNGH0010_sequence_listing.txt

Ser	Gly	Glu	Ser	Gly	Ile	Gln	Gly	Phe	Arg	Gly	Gln	Gly	Val	Ser	Ser		
		55					60					65					
aac	atg	agg	gaa	ata	agc	aaa	gag	ggc	aat	cgc	ctc	ctt	gga	ggc	tct		295
Asn	Met	Arg	Glu	Ile	Ser	Lys	Glu	Gly	Asn	Arg	Leu	Leu	Gly	Gly	Ser		
	70					75					80						
gga	gac	aat	tat	cgg	ggg	caa	ggg	tcg	agc	tgg	ggc	agt	gga	gga	ggg		343
Gly	Asp	Asn	Tyr	Arg	Gly	Gln	Gly	Ser	Ser	Trp	Gly	Ser	Gly	Gly	Gly		
	85				90					95					100		
gac	gct	gtt	ggg	gga	gtc	aat	att	cag	aac	tct	gag	acg	tct	cct	ggg		391
Asp	Ala	Val	Gly	Gly	Val	Asn	Ile	Gln	Asn	Ser	Glu	Thr	Ser	Pro	Gly		
				105					110					115			
atg	ttt	aac	ttt	gac	act	ttc	tgg	aag	aat	ttt	aaa	tcc	aag	ctg	ggg		439
Met	Phe	Asn	Phe	Asp	Thr	Phe	Trp	Lys	Asn	Phe	Lys	Ser	Lys	Leu	Gly		
			120					125					130				
ttc	atc	aac	tgg	gat	gcc	ata	aac	aag	aac	cag	gtc	ccg	ccc	ccc	agc		487
Phe	Ile	Asn	Trp	Asp	Ala	Ile	Asn	Lys	Asn	Gln	Val	Pro	Pro	Pro	Ser		
		135					140					145					
acc	cga	gcc	ctc	ctc	tac	ttc	agc	cga	ctc	tgg	gag	gat	ttc	aaa	cag		535
Thr	Arg	Ala	Leu	Leu	Tyr	Phe	Ser	Arg	Leu	Trp	Glu	Asp	Phe	Lys	Gln		
	150					155					160						
aac	act	cct	ttc	ctc	aac	tgg	aaa	gca	att	att	gag	ggg	gca	gac	gca		583
Asn	Thr	Pro	Phe	Leu	Asn	Trp	Lys	Ala	Ile	Ile	Glu	Gly	Ala	Asp	Ala		
	165				170					175					180		
tca	tca	ctg	cag	aaa	cgt	gca	ggc	aga	gac	gat	cag	ccg	ggg	gca	gga		631
Ser	Ser	Leu	Gln	Lys	Arg	Ala	Gly	Arg	Asp	Asp	Gln	Pro	Gly	Ala	Gly		
				185					190					195			
tgg	cag	gag	gtg	gca	gct	gta	act	tcc	aag	aac	tac	aat	tac	aac	cag		679
Trp	Gln	Glu	Val	Ala	Ala	Val	Thr	Ser	Lys	Asn	Tyr	Asn	Tyr	Asn	Gln		
			200					205					210				
cat	gca	tat	ccc	act	gcc	tat	ggg	ggg	aag	tac	tca	gtc	aag	acc	cct		727
His	Ala	Tyr	Pro	Thr	Ala	Tyr	Gly	Gly	Lys	Tyr	Ser	Val	Lys	Thr	Pro		
		215					220					225					
gca	aag	ggg	gga	gtc	tca	cct	tct	tcc	tcg	gct	tcc	cgg	gtg	caa	cct		775
Ala	Lys	Gly	Gly	Val	Ser	Pro	Ser	Ser	Ser	Ala	Ser	Arg	Val	Gln	Pro		
	230					235					240						
ggc	ctg	ctg	cag	tgg	gtg	aag	ttt	tgg	tag	gcaatttctt gcaaccacca							825
Gly	Leu	Leu	Gln	Trp	Val	Lys	Phe	Trp									
	245				250												
ccgaggcccc	gaaaagcact						ggcgtcagg	gagctcctcc						cttggtcccc	cagcctgtgc		885
cagccctggc	ccggctgcc						cacctctgtt	tcctaggctg						gggacccagc	ttgtctctcc		945
ttgtttcttc	ccactgcact						gtggtgcttc	agtggccacc						agcctcgtca	catacaccag		1005
catctttctg	tacctcctcc						ctttggtgac	ctgaagtcac						tgtgacagtt	ctccaggaag		1065
gaggagcttc	ctacttttga						gtttctctgt	ggaaataaaa						catgaatctt	gtttcccta		1124

CNGH0010_sequence_listing.txt

<211> 253
 <212> PRT
 <213> Homo sapiens

<400> 7

Met Leu Gly Ile Thr Ser Cys Ser Asp Gln Gln Ala Lys Glu Gly Glu
 1 5 10 15

Gly Leu Glu Gly Ser Ser Thr Gly Ser Ser Ser Gly Asn His Gly Gly
 20 25 30

Ser Gly Gly Gly Asn Gly His Lys Pro Gly Cys Glu Lys Pro Gly Asn
 35 40 45

Glu Ala Arg Gly Ser Gly Glu Ser Gly Ile Gln Gly Phe Arg Gly Gln
 50 55 60

Gly Val Ser Ser Asn Met Arg Glu Ile Ser Lys Glu Gly Asn Arg Leu
 65 70 75 80

Leu Gly Gly Ser Gly Asp Asn Tyr Arg Gly Gln Gly Ser Ser Trp Gly
 85 90 95

Ser Gly Gly Gly Asp Ala Val Gly Gly Val Asn Ile Gln Asn Ser Glu
 100 105 110

Thr Ser Pro Gly Met Phe Asn Phe Asp Thr Phe Trp Lys Asn Phe Lys
 115 120 125

Ser Lys Leu Gly Phe Ile Asn Trp Asp Ala Ile Asn Lys Asn Gln Val
 130 135 140

Pro Pro Pro Ser Thr Arg Ala Leu Leu Tyr Phe Ser Arg Leu Trp Glu
 145 150 155 160

Asp Phe Lys Gln Asn Thr Pro Phe Leu Asn Trp Lys Ala Ile Ile Glu
 165 170 175

Gly Ala Asp Ala Ser Ser Leu Gln Lys Arg Ala Gly Arg Asp Asp Gln
 180 185 190

Pro Gly Ala Gly Trp Gln Glu Val Ala Ala Val Thr Ser Lys Asn Tyr
 195 200 205

Asn Tyr Asn Gln His Ala Tyr Pro Thr Ala Tyr Gly Gly Lys Tyr Ser
 210 215 220

Val Lys Thr Pro Ala Lys Gly Gly Val Ser Pro Ser Ser Ser Ala Ser
 Page 25

[illegible]

CNGH0010_sequence_listing.txt

<210> 9
 <211> 149
 <212> PRT
 <213> Homo sapiens

<400> 9

Met Leu Gly Ile Thr Ser Cys Ser Asp Gln Gln Ala Lys Glu Gly Glu
 1 5 10 15

Gly Leu Glu Gly Ser Ser Thr Gly Ser Ser Ser Gly Asn His Gly Gly
 20 25 30

Ser Gly Gly Gly Asn Gly His Lys Pro Gly Cys Glu Lys Pro Gly Asn
 35 40 45

Glu Ala Arg Gly Ser Gly Glu Ser Gly Ile Gln Gly Phe Arg Gly Gln
 50 55 60

Gly Val Ser Ser Asn Met Arg Glu Ile Ser Lys Glu Gly Asn Arg Leu
 65 70 75 80

Leu Gly Gly Ser Gly Asp Asn Tyr Arg Gly Gln Gly Ser Ser Trp Gly
 85 90 95

Ser Gly Gly Gly Asp Ala Val Gly Gly Val Asn Ile Gln Asn Ser Glu
 100 105 110

Thr Ser Pro Gly Met Phe Asn Phe Asp Thr Phe Trp Lys Asn Phe Lys
 115 120 125

Ser Lys Leu Gly Phe Ile Asn Trp Asp Ala Ile Asn Lys Asp Gln Arg
 130 135 140

Ser Ser Arg Ile Pro
 145

<210> 10
 <211> 600
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (6)..(272)

<400> 10
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 Met Lys Pro Ala Thr Ala Ser Ala Leu Leu Leu Leu Leu Gly
 1 5 10 15

CNGH0010_sequence_listing.txt

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ctg gcc tgg acc cag ggg agc cac ggc tgg ggt gcg gac gcg tca tca      98
Leu Ala Trp Thr Gln Gly Ser His Gly Trp Gly Ala Asp Ala Ser Ser
                20                25                30

ctg cag aaa cgt gca ggc aga gac gat cag aac tac aat tac aac cag      146
Leu Gln Lys Arg Ala Gly Arg Asp Asp Gln Asn Tyr Asn Tyr Asn Gln
                35                40                45

cat gcg tat ccc act gcc tat ggt ggg aag tac tca gtc aag acc cct      194
His Ala Tyr Pro Thr Ala Tyr Gly Gly Lys Tyr Ser Val Lys Thr Pro
                50                55                60

gca aag ggg gga gtc tca cct tct tcc tcg gct tcc cgg gtg caa cct      242
Ala Lys Gly Gly Val Ser Pro Ser Ser Ser Ala Ser Arg Val Gln Pro
                65                70                75

ggc ctg ctg cag tgg gtg aag ttt tgg tag gcaatttctt gcaaccacca      292
Gly Leu Leu Gln Trp Val Lys Phe Trp
80                85

ccgaggcccc gaaaagcact ggctcgtcagg gagctcctcc ccttggcccc cagcctgtgc      352

cagccctggc ccggctgcca cacctctgtt tcctaggctg gggaccagc ttgtctctcc      412

ttgtttcttc ccactgcact gtggtgcttc agtggccacc agcctcgtca catacaccag      472

catctttctg tacctcctcc ctttggtgac ctgaagtcac tgtgacagtt ctccaggaag      532

gaggagcttc ctacttttga gtttctctgt ggaaataaaa catgaatctt gtttccttaa      592

aaaaaaaaa                                                                600

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<210> 11
 <211> 88
 <212> PRT
 <213> Homo sapiens

<400> 11

Met Lys Pro Ala Thr Ala Ser Ala Leu Leu Leu Leu Leu Gly Leu
 1 5 10 15

Ala Trp Thr Gln Gly Ser His Gly Trp Gly Ala Asp Ala Ser Ser Leu
 20 25 30

Gln Lys Arg Ala Gly Arg Asp Asp Gln Asn Tyr Asn Tyr Asn Gln His
 35 40 45

Ala Tyr Pro Thr Ala Tyr Gly Gly Lys Tyr Ser Val Lys Thr Pro Ala
 50 55 60

Lys Gly Gly Val Ser Pro Ser Ser Ser Ala Ser Arg Val Gln Pro Gly
 65 70 75 80

Leu Leu Gln Trp Val Lys Phe Trp
 85

CNGH0010_sequence_listing.txt

<210> 12
<211> 24
<212> DNA
<213> Homo sapiens

<400> 12
ggctgggcag agatgaagtt ccag 24

<210> 13
<211> 20
<212> DNA
<213> Homo sapiens

<400> 13
tctgcctggg cagtggggag 20

<210> 14
<211> 25
<212> DNA
<213> Homo sapiens

<400> 14
atgctcgga taacttcctg cagcg 25

<210> 15
<211> 21
<212> DNA
<213> Homo sapiens

<400> 15
gcagcgacca acaggctaaa g 21

<210> 16
<211> 22
<212> DNA
<213> Homo sapiens

<400> 16
atgaagccgg ccactgcctc tg 22

<210> 17
<211> 20
<212> DNA
<213> Homo sapiens

<400> 17
ctctgctcct gctcctgctg 20

<210> 18
<211> 20
<212> DNA
<213> Homo sapiens

<400> 18
gggccagggc tggcacaggc 20

CNGH0010_sequence_listing.txt

<210> 19	
<211> 21	
<212> DNA	
<213> Homo sapiens	
<400> 19	
cggggcctcg gtggtggttg c	21
<210> 20	
<211> 25	
<212> DNA	
<213> Homo sapiens	
<400> 20	
tctggtggct ccttgtctgg aggtc	25
<210> 21	
<211> 28	
<212> DNA	
<213> Homo sapiens	
<400> 21	
gtcacgggat gcgagagctt ctctggtc	28
<210> 22	
<211> 17	
<212> DNA	
<213> Homo sapiens	
<400> 22	
gcttttcaca cccgggt	17
<210> 23	
<211> 20	
<212> DNA	
<213> Homo sapiens	
<400> 23	
ggcggaggaa atggacataa	20
<210> 24	
<211> 26	
<212> DNA	
<213> Homo sapiens	
<400> 24	
gcttgattt aaaattcttc cagaaa	26
<210> 25	
<211> 21	
<212> DNA	
<213> Homo sapiens	
<400> 25	
gaggtagacag cggcagtgag t	21

CNGH0010_sequence_listing.txt

<210> 26	
<211> 30	
<212> DNA	
<213> Homo sapiens	
<400> 26	
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<210> 27	
<211> 20	
<212> DNA	
<213> Homo sapiens	
<400> 27	
attcagaact ctgagacgtc	20
<210> 28	
<211> 26	
<212> DNA	
<213> Homo sapiens	
<400> 28	
tgttggtgga gtcaatactg tgaact	26
<210> 29	
<211> 19	
<212> DNA	
<213> Homo sapiens	
<400> 29	
cgggatgcca gagcttctc	19
<210> 30	
<211> 24	
<212> DNA	
<213> Homo sapiens	
<400> 30	
cactttctgg aagaatttta aatc	24
<210> 31	
<211> 17	
<212> DNA	
<213> Homo sapiens	
<400> 31	
ggagcggcgg aggaaat	17
<210> 32	
<211> 21	
<212> DNA	
<213> Homo sapiens	
<400> 32	
tgatgaaacc cagcttggat t	21

CNGH0010_sequence_listing.txt

<210> 33
<211> 20
<212> DNA
<213> Homo sapiens

<400> 33
aaaccggga actctgagac 20

<210> 34
<211> 21
<212> DNA
<213> Homo sapiens

<400> 34
ggcggaggaa atggacataa a 21

<210> 35
<211> 25
<212> DNA
<213> Homo sapiens

<400> 35
gagcttctct ggtccttggt tatgg 25

<210> 36
<211> 19
<212> DNA
<213> Homo sapiens

<400> 36
aatctgggat tcagaactc 19

<210> 37
<211> 17
<212> DNA
<213> Homo sapiens

<400> 37
gggtgcggac gcgtcat 17

<210> 38
<211> 27
<212> DNA
<213> Homo sapiens

<400> 38
gtcttgactg agtacttccc accatag 27

<210> 39
<211> 23
<212> DNA
<213> Homo sapiens

<400> 39
acgatcagaa ctacaattac aac 23

CNGH0010_sequence_listing.txt