CGRP ANTIBODIES

The present invention is in the field of medicine, particularly in the field of antibodies to calcitonin gene-related peptide (CGRP). More specifically, the invention relates to CGRP antibodies and the use of the CGRP antibodies for therapy of osteoarthritis pain or migraines

Calcitonin gene related peptide (CGRP) is a 37 amino acid neuropeptide secreted by the nerves of the central and peripheral nervous systems. CGRP is widely distributed in sensory nerves, both in the peripheral and central nervous system and displays a large number of different biological activities. CGRP is reported to play a role. When released from trigeminal and other nerve fibers, CGRP is thought to mediate its biological responses by binding to specific cell surface receptors.

CGRP has been reported to play a role in migraines as CGRP is released upon stimulation of sensory nerves and has potent vasodilatory activity. The release of CGRP increases vascular permeability and subsequent plasma protein leakage (plasma protein extravasation) in tissues innervated by trigeminal nerve fibers upon stimulation of these fibers. In addition, studies have reported that infusion of CGRP in patients who suffer from migraines has resulted in migraine-like symptoms.

CGRP is also reported to play a role in osteoarthritis (OA). OA is a chronic condition that affects a large percentage of people worldwide. Pain in arthritis is characterized by hyperalgesia (overly sensitive to normally non-noxious stimuli) and spontaneous pain (pain at rest). Inflammation of the joint causes peripheral and central sensitization. In peripheral sensitization, the normally high-threshold CGRP-containing nociceptors begin to respond to light pressure associated with normal joint movement. CGRP acts as a local facilitator of inflammatory processes. This continued process eventually leads to central sensitization in the spinal cord such that neurons become responsive to stimulation of inflamed as well as non-inflamed tissue. In preclinical models of OA pain in the rat, an increase in the number of CGRP positive nerve fibers was observed, positively correlating with the amount of pain.

Current standard of care for OA pain consists of non-steroidal anti-inflammatory drugs (NSAIDs) and selective Cox-2 inhibitors. Over time, many patients will become insensitive to these treatments or are not able to tolerate the high doses needed for effective pain relief. Follow-up treatments consist of intra-articular injections (hyaluronan) or opiates. The final treatment is surgical total joint replacement. Many of these treatments have negative side effects, ranging from gastro-intestinal (NSAIDs) to cardiovascular (Cox-2 inhibitors), are cumbersome and/or not very efficacious (intra-articular injections), carry the risk for abuse (opiates), or are restricted to only 1 joint (intra-articular injections, surgery).

Although CGRP antibodies for treating migraines and for treating inflammation pain have been disclosed (migraines-WO 2007/076336 and WO 2007/054809; OA-see, Antibody G1 of WO2009/109908A1), there is still a need for alternatives. Preferably, the treatment alternative is safe and efficacious. More preferably, the alternative treatment for OAwill provide long-lasting pain relief across multiple joints that is tolerable to patients without the risk for dependence and/or abuse.

The present invention provides a human engineered CGRP antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR comprises LCDR1, LCDR2, and LCDR3 amino acid sequences and HCVR comprises HCDR1, HCDR2, and HCDR3 amino acid sequences which are selected from the group consisting of:

a) LCDR1 is RASQDIDNYLN (SEQ ID NO: 3), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGDTRYIQKFAG (SEQ ID NO: 13), and HCDR3 is LSDYVSGFSY (SEQ ID NO: 14);

b) LCDR1 is RASQDIDNYLN (SEQ ID NO: 3), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFSY (SEQ ID NO: 14);

c) LCDR1 is RASKDISKYLN (SEQ ID NO: 6), LCDR2 is YTSGYHS (SEQ ID NO: 7), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAD (SEQ ID NO: 16), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39);

d) LCDR1 is RASRPIDKYLN (SEQ ID NO: 8), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39); and

e) LCDR1 is RASQDIDKYLN (SEQ ID NO: 9), LCDR2 is YTSGYHS (SEQ ID NO: 7), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39),

wherein the human engineered CGRP antibody binds to human CGRP.

The present invention provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 3, LCDR2 is SEQ ID NO: 4, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 13, and HCDR3 is SEQ ID NO: 14, wherein the human engineered CGRP antibody binds to human CGRP. The present invention provides a human engineered CGRP antibody or antigen-binding fragment thereof comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 3, LCDR2 is SEQ ID NO: 4, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 15, and HCDR3 is SEQ ID NO: 14, wherein the human engineered CGRP antibody binds to human CGRP. The present invention provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 16, and HCDR3 is SEQ ID NO: 39, wherein the human engineered CGRP antibody binds to human CGRP. The present invention provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 8, LCDR2 is SEQ ID NO: 4, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 15, and HCDR3 is SEQ ID NO: 39,

wherein the human engineered CGRP antibody binds to human CGRP. The present invention provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 9, LCDR2 is SEQ ID NO: 7, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 15, and HCDR3 is SEQ ID NO: 39, wherein the human engineered CGRP antibody binds to human CGRP.

The present invention provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is $RASX_1X_2IX_3X_4YLN$ (SEQ ID NO: 10), LCDR2 is $YTSX_5YHS$ (SEQ ID NO: 11), LCDR3 is QQGDALPPT(SEQ ID NO: 5) and HCDR1 is GYTFGNYWMQ (SEQ ID NO:12), HCDR2 is $AIYEGTGX_6TX_7YIQKFAX_8$ (SEQ ID NO: 37), and HCDR3 is $LSDYVSGFX_9Y$ (SEQ ID NO: 38), wherein X_1 is Q, R, or K; X_2 is D or P, X_3 is D or S, X_4 is N or K, X_5 is G or E, X_6 is K or D, X_7 is V or R, X_8 is D or G, and X_9 is G or S, wherein the antibody binds to human CGRP.

In another embodiment, the present invention provides a human engineered CGRP antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises

$DIQMTQSPSSLSASVGDRVTITCRASX_1X_2IX_3X_4YLNWYQQKPGKAPKLLIYYTSX_5$ $YHSGVPSRFSGSGSGTDFTX_6TISSLQPEDX_7ATYYCQQGDALPPTFGX_8GTKX_9EIK$ wherein X_1 is Q, K, or R; X_2 is D or P; X_3 is D or S; X_4 is K or N; X_5 is E or G; X_6 is F or L; X_7 is I or F; X_8 is Q or G; and X_9 is L or V. (SEQ ID NO: 42)

and the HCVR comprises

$QVQLVQSGAEVKKPGX_1SVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI$ $YEGTGX_2TX_3YIQKFAX_4RVTX_5TX_6DX_7STSTX_8YMELSSLRSEDTAVYYCARLSDY$ $VSGFX_9YWGQGTX_{10}VTVSS$, wherein X_1= A or S; X_2= K or D; X_3=V or R; X_4= G or D; X_5= M or I; X_6=R or A; X_7=T or K; X_8=V or A; X_9=G or S; and X_{10}=L or T. (SEQ ID NO: 43), wherein the antibody binds to human CGRP.

In another embodiment, the present invention provides a human engineered CGRP antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR and HCVR are amino acid sequences selected from the group consisting of:

a. LCVR is SEQ ID NO: 17 and HCVR is SEQ ID NO: 22;
b. LCVR is SEQ ID NO: 18 and HCVR is SEQ ID NO: 23;
c. LCVR is SEQ ID NO: 19 and HCVR is SEQ ID NO: 24;
d. LCVR is SEQ ID NO: 20 and HCVR is SEQ ID NO: 25; and
e. LCVR is SEQ ID NO: 21 and HCVR is SEQ ID NO: 26.

The present invention provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 17 and an HCVR of SEQ ID NO: 22. In a preferred embodiment, the present invention provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 18 and an HCVR of SEQ ID NO: 23. The present invention provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 19 and an HCVR of SEQ ID NO: 24. The present invention provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 20 and an HCVR of SEQ ID NO: 25. The present invention provides a human engineered CGRP antibody comprising a LCVR of SEQ ID NO: 21 and an HCVR of SEQ ID NO: 26.

The present invention also provides a human engineered CGRP antibody comprising a light chain (LC) and a heavy chain (HC), wherein the LC and HC amino acid sequences are selected from the group consisting of:

a) LC is SEQ ID NO: 27 and HC is SEQ ID NO: 32;
b) LC is SEQ ID NO: 28 and HC is SEQ ID NO: 33;
c) LC is SEQ ID NO: 29 and HC is SEQ ID NO: 34;
d) LC is SEQ ID NO: 30 and HC is SEQ ID NO: 35; and
e) LC is SEQ OD NO: 31 and HC is SEQ ID NO: 36.

In an embodiment, the human engineered CGRP antibody comprises an LC of SEQ ID NO: 27 and a HC of SEQ ID NO: 32. In another embodiment, the human engineered CGRP antibody comprises an LC of SEQ ID NO: 28 and an HC of SEQ ID NO: 33. In another embodiment, the human engineered CGRP antibody comprises an LC of SEQ ID NO: 29 and an HC of SEQ ID NO: 34. In another embodiment, the human engineered CGRP antibody comprises an LC of SEQ ID NO: 30 and an HC of SEQ ID NO: 35. In another embodiment, the human engineered CGRP antibody comprises an LC

of SEQ ID NO: 31 and an HC of SEQ ID NO: 36. In an embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 27 and each HC amino acid sequence is SEQ ID NO: 32. In an embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 28 and each HC amino acid sequence is SEQ ID NO: 33. In an embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 29 and each HC amino acid sequence is SEQ ID NO: 34. In a embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 30 and each HC amino acid sequence is SEQ ID NO: 35. In an embodiment, the human engineered CGRP antibody comprises two light chains and two heavy chains wherein each LC amino acid sequence is SEQ ID NO: 31 and each HC amino acid sequence is SEQ ID NO: 36. The present invention also provides antigen-binding fragment of the antibodies described herein.

The present invention also provides human engineered CGRP antibodies which have an IC50 < 1.0 nM in an assay essentially as described in Example 4. In an embodiment, the present invention provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 16, and HCDR3 is SEQ ID NO: 39, and wherein the human engineered CGRP antibody binds to human CGRP and also has an IC50 < 1.0 nM in an assay essentially as described in Example 4. In an embodiment, the present invention provides a human engineered CGRP antibody comprising a LCVR amino acid sequence of SEQ ID NO: 19 and an HCVR amino acid sequence of SEQ ID NO: 24, wherein the human engineered CGRP antibody has an IC50 < 1.0 nM in an assay essentially as described Example 4. In an embodiment, the present invention provides a human engineered CGRP antibody comprising a LC amino acid sequence of SEQ ID NO: 29 and a HC amino acid sequence of SEQ ID NO: 34, wherein the human engineered CGRP antibody has an IC50 < 1.0 nM in an assay essentially as described in Example 4.

The present invention also provides human engineered CGRP antibodies which have an IC50 < 0.5 nM in an assay essentially as described in Example 4. In an embodiment, the present invention provides a human engineered CGRP antibody comprising an LCVR and an HCVR wherein LCDR1 is SEQ ID NO: 6, LCDR2 is SEQ ID NO: 7, LCDR3 is SEQ ID NO: 5, HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 16, and HCDR3 is SEQ ID NO: 39, and wherein the human engineered CGRP antibody binds to human CGRP and also has an IC50 < 0.5 nM nM in an assay essentially as described in Example 4. In an embodiment, the present invention provides a human engineered CGRP antibody comprising a LCVR amino acid sequence of SEQ ID NO: 19 and an HCVR amino acid sequence of SEQ ID NO: 24, wherein the human engineered CGRP antibody has an IC50 < 0.5 nM nM in an assay essentially as described Example 4. In an embodiment, the present invention provides a human engineered CGRP antibody comprising a LC amino acid sequence of SEQ ID NO: 29 and a HC amino acid sequence of SEQ ID NO: 34, wherein the human engineered CGRP antibody has an IC50 < 0.5 nM nM in an assay essentially as described in Example 4.

The present invention also provides a pharmaceutical composition comprising a human engineered CGRP antibody or antigen-binding fragment thereof of the present invention and a pharmaceutically acceptable carrier, diluent or excipient. The present invention further provides a pharmaceutical composition comprising a CGRP antibody of the present invention together with a pharmaceutically acceptable carrier and optionally, other therapeutic ingredients.

In a further aspect, the present invention provides a method of treating osteoarthritis pain comprising administering to a patient in need thereof a human engineered CGRP antibody or antigen-binding fragment thereof of the present invention. In another aspect, the present invention provides a method of treating migraines comprising administering to a patient in need thereof a human engineered CGRP antibody or antigen-binding fragment thereof of the present invention

The present invention also provides a human engineered CGRP antibody or antigen-binding fragment thereof of the present invention for use in therapy. In another

aspect, the present invention provides a human engineered CGRP antibody or antigen-binding fragment thereof of the present invention for the treatment of osteoarthritis pain. In a further aspect, the present invention provides a human engineered CGRP antibody or antigen-binding fragment thereof of the present invention for the treatment of migraines.

The present invention also provides the use of a human engineered CGRP antibody or antigen-binding fragment thereof of the present invention for use in the treatment of osteoarthritis pain. In another aspect, the present invention also provides the use of a human engineered CGRP antibody or antigen-binding fragment thereof of the present invention for use in the treatment of migraines. The present invention also provides the use of a human engineered CGRP antibody or antigen binding fragment thereof in the manufacture of a medicament for the treatment of osteoarthritis. The present invention also provides the use of a human engineered CGRP antibody or antigen binding fragment thereof in the manufacture of a medicament for the treatment of migraines.

A full-length antibody as it exists naturally is an immunoglobulin molecule comprising 2 heavy (H) chains and 2 light (L) chains interconnected by disulfide bonds. The amino terminal portion of each chain includes a variable region of about 100-110 amino acids primarily responsible for antigen recognition via the complementarity determining regions (CDRs) contained therein. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function.

The CDRs are interspersed with regions that are more conserved, termed framework regions (FR). Each light chain variable region (LCVR) and heavy chain variable region (HCVR) is composed of 3 CDRs and 4 FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The 3 CDRs of the light chain are referred to as "LCDR1, LCDR2, and LCDR3" and the 3 CDRs of the heavy chain are referred to as "HCDR1, HCDR2, and HCDR3." The CDRs contain most of the residues which form specific interactions with the antigen. The numbering and positioning of CDR amino acid residues within the

LCVR and HCVR regions is in accordance with the well-known Kabat numbering convention.

Light chains are classified as kappa or lambda, and are characterized by a particular constant region as known in the art. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, and define the isotype of an antibody as IgG, IgM, IgA, IgD, or IgE, respectively. IgG antibodies can be further divided into subclasses, e.g., IgG1, IgG2, IgG3, IgG4. Each heavy chain type is characterized by a particular constant region with a sequence well known in the art.

As used herein, the term "monoclonal antibody" (Mab) refers to an antibody that is derived from a single copy or clone including, for example, any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Mabs of the present invention preferably exist in a homogeneous or substantially homogeneous population. Complete Mabs contain 2 heavy chains and 2 light chains. "Antigen-binding fragments" of such monoclonal antibodies include, for example, Fab fragments, Fab' fragments, $F(ab')_2$ fragments, and single chain Fv fragments. Monoclonal antibodies and antigen-binding fragments thereof of the present invention can be produced, for example, by recombinant technologies, phage display technologies, synthetic technologies, e.g., CDR-grafting, or combinations of such technologies, or other technologies known in the art. For example, mice can be immunized with human CGRP or fragments thereof, the resulting antibodies can be recovered and purified, and determination of whether they possess binding and functional properties similar to or the same as the antibody compounds disclosed herein can be assessed by the methods disclosed in Examples below. Antigen-binding fragments can also be prepared by conventional methods. Methods for producing and purifying antibodies and antigen-binding fragments are well known in the art and can be found, for example, in Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, chapters 5-8 and 15, ISBN 0-87969-314-2.

The phrase "human engineered CGRP antibodies" refers to monoclonal antibodies created and/or manipulated to have binding and functional properties according to the

invention, bind to human CGRP, and that have framework regions that are substantially human or fully human surrounding CDRs derived from a non-human antibody. "Antigen-binding fragments" of such human engineered antibodies include, for example, Fab fragments, Fab' fragments, $F(ab')_2$ fragments, and single chain Fv fragments. "Framework region" or "framework sequence" refers to any one of framework regions 1 to 4. Human engineered antibodies and antigen-binding fragments thereof encompassed by the present invention include molecules wherein any one or more of framework regions 1 to 4 is substantially or fully human, i.e., wherein any of the possible combinations of individual substantially or fully human framework regions 1 to 4, is present. For example, this includes molecules in which framework region 1 and framework region 2, framework region 1 and framework region 3, framework region 1, 2, and 3, etc., are substantially or fully human. Substantially human frameworks are those that have at least about 80% sequence identity to a known human germline framework sequence. Preferably, the substantially human frameworks have at least about 85%, about 90%, about 95%, or about 99% sequence identity to a known human germline framework sequence.

Fully human frameworks are those that are identical to a known human germline framework sequence. Human framework germline sequences can be obtained from ImMunoGeneTics (IMGT) via their website http://imgt.cines.fr, or from *The Immunoglobulin FactsBook* by Marie-Paule Lefranc and Gerard Lefranc, Academic Press, 2001, ISBN 012441351. For example, germline light chain frameworks can be selected from the group consisting of: A11, A17, A18, A19, A20, A27, A30, L1, L11, L12, L2, L5, L15, L6, L8, O12, O2, and O8, and germline heavy chain framework regions can be selected from the group consisting of: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VHI-46, VH3-9, VH3-66, VH3-74, VH4-31, VHI-18, VHI-69, VI-13-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51.

Human engineered antibodies in addition to those disclosed herein exhibiting similar functional properties according to the present invention can be generated using several different methods. The specific antibody compounds disclosed herein can be used as templates or parent antibody compounds to prepare additional antibody compounds. In

one approach, the parent antibody compound CDRs are grafted into a human framework that has a high sequence identity with the parent antibody compound framework. The sequence identity of the new framework will generally be at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% identical to the sequence of the corresponding framework in the parent antibody compound. This grafting may result in a reduction in binding affinity compared to that of the parent antibody. If this is the case, the framework can be back-mutated to the parent framework at certain positions based on specific criteria disclosed by Queen et al. (1991) *Proc. Natl. Acad. Sci. USA* 88:2869. Additional references describing methods useful in humanizing mouse antibodies include U.S. Patent Nos. 4,816,397; 5,225,539, and 5,693,761; computer programs ABMOD and ENCAD as described in Levitt (1983) *J. Mol. Biol.* 168:595-620; and the method of Winter and co-workers (Jones et al. (1986) *Nature* 321:522-525; Riechmann et al. (1988) *Nature* 332:323-327; and Verhoeyen et al. (1988) *Science* 239:1534-1536.

The identification of residues to consider for back-mutation can be carried out as follows:

When an amino acid falls under the following category, the framework amino acid of the human germ-line sequence that is being used (the "acceptor framework") is replaced by a framework amino acid from a framework of the parent antibody compound (the "donor framework"):

(a) the amino acid in the human framework region of the acceptor framework is unusual for human frameworks at that position, whereas the corresponding amino acid in the donor immunoglobulin is typical for human frameworks at that position;

(b) the position of the amino acid is immediately adjacent to one of the CDRs; or

(c) any side chain atom of a framework amino acid is within about 5-6 angstroms (center-to-center) of any atom of a CDR amino acid in a three dimensional immunoglobulin model.

When each of the amino acids in the human framework region of the acceptor framework and a corresponding amino acid in the donor framework is generally unusual for human frameworks at that position, such amino acid can be replaced by an amino acid typical for human frameworks at that position. This back-mutation criterion enables one to recover the activity of the parent antibody compound.

Another approach to generating human engineered antibodies exhibiting similar functional properties to the antibody compounds disclosed herein involves randomly mutating amino acids within the grafted CDRs without changing the framework, and screening the resultant molecules for binding affinity and other functional properties that are as good as or better than those of the parent antibody compounds. Single mutations can also be introduced at each amino acid position within each CDR, followed by assessing the effects of such mutations on binding affinity and other functional properties. Single mutations producing improved properties can be combined to assess their effects in combination with one another.

Further, a combination of both of the foregoing approaches is possible. After CDR grafting, one can back-mutate specific framework regions in addition to introducing amino acid changes in the CDRs. This methodology is described in Wu et al. (1999) *J. Mol. Biol.* 294:151-162.

Applying the teachings of the present invention, a person skilled in the art can use common techniques, e.g., site-directed mutagenesis, to substitute amino acids within the presently disclosed CDR and framework sequences and thereby generate further variable region amino acid sequences derived from the present sequences. All alternative naturally occurring amino acids can be introduced at a specific substitution site. The methods disclosed herein can then be used to screen these additional variable region amino acid sequences to identify sequences having the indicated *in vivo* functions. In this way, further sequences suitable for preparing human engineered antibodies and antigen-

binding portions thereof in accordance with the present invention can be identified. Preferably, amino acid substitution within the frameworks is restricted to one, two, or three positions within any one or more of the 4 light chain and/or heavy chain framework regions disclosed herein. Preferably, amino acid substitution within the CDRs is restricted to one, two, or three positions within any one or more of the 3 light chain and/or heavy chain CDRs. Combinations of the various changes within these framework regions and CDRs described above are also possible.

The term "treating" (or "treat" or "treatment") refers to processes involving a slowing, interrupting, arresting, controlling, stopping, reducing, or reversing the progression or severity of a symptom, disorder, condition, or disease, but does not necessarily involve a total elimination of all disease-related symptoms, conditions, or disorders associated with CGRP activity.

The term "migraine(s)" as used herein refers to "migraines without aura" (formerly "common migraine") and "migraines with aura" (formerly "classical migraines") according to the Headache Classification Committee of the International Headache Society (International Headache Society, 2004). For example, "migraines without aura", typically may be characterized as having a pulsating quality, a moderate or severe intensity, are aggravated by routine physical activity, are unilaterally located and are associated with nausea and with photophobia and phonophobia. "Migraines with aura" may include disturbances in vision, disturbances in other senses, unilateral weakness, and in some instances difficulty with speech.

The human engineered antibodies of the present invention can be used as medicaments in human medicine, administered by a variety of routes. Most preferably, such compositions are for parenteral administration. Such pharmaceutical compositions can be prepared by methods well known in the art (*See*, e.g., *Remington: The Science and Practice of Pharmacy*, 19th ed. (1995), A. Gennaro et al., Mack Publishing Co.) and comprise a human engineered antibody as disclosed herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

The results of the following assays demonstrate that the exemplified monoclonal antibodies and antigen-binding fragments thereof of the present invention may be used for treating osteoarthritis pain.

Example 1-Production of Antibodies

Antibodies I-V can be made and purified as follows. An appropriate host cell, such as HEK 293 EBNA or CHO, is either transiently or stably transfected with an expression system for secreting antibodies using an optimal predetermined HC:LC vector ratio or a single vector system encoding both LC, such as SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, or SEQ ID NO: 31, and HC, such as SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35 or SEQ ID NO: 36. Clarified media, into which the antibody has been secreted, is purified using any of many commonly-used techniques. For example, the medium may be conveniently applied to a Protein A or G Sepharose FF column that has been equilibrated with a compatible buffer, such as phosphate buffered saline (pH 7.4). The column is washed to remove nonspecific binding components. The bound antibody is eluted, for example, by pH gradient (such as 0.1 M sodium phosphate buffer pH 6.8 to 0.1 M sodium citrate buffer pH 3.0). Antibody fractions are detected, such as by SDS-PAGE, and then are pooled. Further purification is optional, depending on the intended use. The antibody may be concentrated and/or sterile filtered using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion, hydrophobic interaction, ion exchange, or hydroxyapatite chromatography. The purity of the antibody after these chromatography steps is greater than 99%. The product may be immediately frozen at -70°C or may be lyophilized. The amino acid sequences for these exemplified antibodies are provided below.

Table 1-Antibody SEQ ID NOs

Antibody	Heavy Chain	Light Chain	LCVR	HCVR
I	32	27	17	22

II	33	28	18	23
III	34	29	19	24
IV	35	30	20	25
V	36	31	21	26

Antibody	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
I	12	13	14	3	4	5
II	12	15	14	3	4	5
III	12	16	39	6	7	5
IV	12	15	39	8	4	5
V	12	15	39	9	7	5

EXAMPLE 2: Affinity (Kd) Measurements for Human Engineered CGRP antibodies

Binding affinity of the exemplified antibodies to CGRP is determined using a surface plasmon resonance assay on a Biacore T100 instrument primed with HBS-EP+ (GE Healthcare, 10 mM Hepes pH7.4 + 150 mM NaCl + 3 mM EDTA + 0.05% surfactant P20) running buffer and analysis temperature set at 37 °C. A CM5 chip containing immobilized protein A (generated using standard NHS-EDC amine coupling) on all four flow cells (Fc) is used to employ a capture methodology. Antibody samples are prepared at 2 μg/mL by dilution into running buffer. Human CGRP samples are prepared at final concentrations of 5.0, 2.5, 1.3, 0.63, 0.31, and 0 (blank) nM by dilution into running buffer. A fresh, single-use aliquot of CGRP is used for each replicate experiment to avoid multiple freeze-thaw cycles. Each analysis cycle consists of (1) capturing antibody samples on separate flow cells (Fc2, Fc3, and Fc4), (2) injection of 350 μL (210-sec) of CGRP over all Fc at 100 μL/min, (3) return to buffer flow for 10 min

to monitor dissociation phase, (4) regeneration of chip surfaces with a 5 µL (15-sec) injection of glycine, pH1.5, (5) equilibration of chip surfaces with a 5 µL (15-sec) injection of HBS-EP+. Each CGRP concentration is injected in duplicate. Data are processed using standard double-referencing and fit to a 1:1 binding model using Biacore T100 Evaluation software, version 2.0.1, to determine the association rate (k_{on}, $M^{-1}s^{-1}$ units), dissociation rate (k_{off}, s^{-1} units), and Rmax (RU units). The equilibrium dissociation constant (K_D) is calculated as from the relationship $K_D = k_{off}/k_{on}$, and is in molar units. Values provided in Table 2 are means of n number of experiments. Table 2 demonstrates that the exemplified antibodies of the present invention bind to CGRP with affinities < 200 pM.

Table 2- Antibody Binding Affinities.

Antibody	K_D (pM) Mean ± SD	n
I	190	1
II	26 ± 6	3
III	31 ± 19	6
IV	24 ± 10	4
V	24 ± 6	2

EXAMPLE 3- Reduction of Pain in an MIA model.

The injection of monoiodoacetic acid (MIA) into the knee joint of rats produces an acute inflammatory insult which then develops into chronic degeneration of the joint tissues in the injected joint. The pain resulting from the joint injury can be measured via differential weight bearing of the hind legs using an incapacitance tester. The MIA model has been well-described in the literature and has been used to demonstrate efficacy vs. pain for a variety of mechanisms and compounds. Efficacy is routinely measured by the ability of a compound to partially normalize weight distribution.

To determine the ability of the exemplified antibodies of the present invention to reduce pain, male Lewis rats (Harlan, Indianapolis, IN) of approximately eight weeks of age at the time of MIA injection are used. The rats are housed in groups of two or three per cage and maintained in a constant temperature and on a 12 hour light/12 hour dark cycle. Animals have free access to food and water at all times except during data collection. All experiments are carried out according to protocols approved by the Eli Lilly Institutional Animal Care and Use Committee.

The right knees of each rat are injected with 0.3 mg MIA in 50 µL of saline and the left knees with 50 µL of saline on day 0. On a set day post MIA, human IgG4 control or test CGRP antibody is subcutaneously administered in PBS (n= 6 per group). Three days post dosing with test CGRP antibody, pain is measured using incapacitance testing which measures the difference in hind paw weight bearing between the MIA treated and saline injected knees. Each measurement is the average of three separate measurements each measured over 1 second.

Data are presented as percent inhibition of pain calculated by dividing the mean of the CGRP antibody treated group by the mean of the control antibody group, subtracting this value from 1 and multiplying this resulting value by 100. CGRP treated groups are also compared to vehicle groups by one way analysis of means and Dunnett's test using JMP (versions 5.1 and 6) statistical analysis program (SAS Institute Inc., Cary, NC). Differences are considered to be significant if the P value is less than 0.05. As shown in Table 3, the data demonstrate that the exemplified CGRP antibodies of the present invention significantly reduce pain.

Table 3- Percent Inhibition of MIA Induced Pain

Antibody	Dose and route	MIA % inhibition	Significant by Dunnett's test ($p<0.05$)
I	20mg/kg sc	20%	Yes
II	4mg/kg sc	30%	Yes
III	4mg/kg sc	37%	Yes
IV	4mg/kg sc	37%	Yes
V	4mg/kg sc	19%	yes

EXAMPLE 4-Inhibition of CGRP induced cAMP formation in SK-N-MC cells

To compare the ability of an antibody of the present invention to Antibody G1 (LCVR- SEQ ID NO: 40 and HCVR- SEQ ID NO: 41), inhibition of CGRP induced cAMP formation in SK-N-MC is determined. Binding of CGRP to its receptor results in the stimulation of cAMP production. The CGRP receptor is a hetero-trimeric complex consisting of the Calcitonin receptor-Like Receptor (CLR, a G-protein coupled receptor) and Receptor Activity Modifying Protein (RAMP)-1, coupled cytoplasmically to Receptor Component Protein (RCP). The human neuroepithelioma cell line SK-N-MC expresses these 3 molecules naturally and can therefore be used to assess the effect of CGRP on signal transduction events. Production of cAMP is a standard measure for G-protein coupled receptor activation.

SK-N-MC cells are cultured in MEM, containing 10% FBS, 1X MEM non-essential amino acids, 1X 100 mM MEM Sodium Pyruvate, 1X Pen/Strep, and 2 mM L-glutamine. After harvesting, cells are washed once and resuspended in assay buffer (stimulation buffer (HBSS with Mg and Ca, 5 mM HEPES, 0.1 % BSA, 100 uM Ascorbic acid) diluted 1:2 with Dulbecco's PBS containing a final concentration of 0.5 mM IBMX) and plated in 96-well plates at 15,000 cells per well. Test antibody or a control human IgG4 antibody are added (serial 4-fold dilutions in assay buffer, 10 concentrations) to the cells, followed by a fixed amount of human α-CGRP (2 nM; Bachem H1470). Plates are incubated for 1 hr at room temperature. Levels of cAMP are measured by a homogeneous time resolved fluorescence (HTRF) assay system (Cisbio).

The amount of cAMP induced by 2 nM human CGRP in the presence of varying concentrations of antibody is calculated as a percentage inhibition compared to CGRP alone. The antibody concentration producing 50% inhibition of cAMP production (IC50) is then calculated from a 4-parameter curve fit model. Following the procedures as described herein, Antibody III (IC_{50} of 0.41 nM) inhibited the amount of CGRP induced cAMP to a much greater extent than Antibody G1 (IC_{50} of 5.36 nM) possibly due to Antibody III's faster K_{on} rate (K_{on} rate as measured by Biacore)

EXAMPLE 5- Rat Dural Plasma Protein Extravasation (PPE) Model

The rat PPE model is a well established pre-clinical model that may be used to evaluate the efficacy of anti-CGRP antibodies for the treatment of migraine.

A 2 mg/mL solution of an anti-CGRP antibody (Ab) is prepared in saline solution. All subsequent dilutions are made with saline. A 2 mg/mL solution of monoclonal isotype control antibody (IgG) is also prepared in saline.

Male Sprague-Dawley rats from Harlan Laboratories (250 to 350 g) are anesthetized with Nembutal (60 mg/kg, ip.) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at –2.5 mm. Following a mid-line sagittal scalp incision, two pairs of bilateral holes are drilled through the skull (3.2 mm posteriorly, 1.8 and 3.8 mm laterally, all coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes (Rhodes Medical Systems Inc), insulated except at the tips, are lowered through the holes in both hemispheres to a depth of 9.2 mm below the dura. Test antibodies or saline vehicle are administered intravenously via the femoral vein (1 mL/kg). Eight minutes later a solution of fluoroscein isothiocyanate (FITC) dye-labeled bovine serum albumin (BSA) (FITC-BSA, Sigma A9771) (20 mg/kg, iv.) is injected into the femoral vein to function as a marker for protein extravasation. Ten minutes following dosing with test antibodies or vehicle, the left trigeminal ganglion is stimulated for 5minutes at a current intensity of 1.0 mA (5 Hz, 5 ms duration) with a Model S48 Grass Instrument Stimulator. Five minutes following stimulation, the rats are killed by exsanguination with 40 mL of saline. The exsanguination also rinses residual FITC/BSA out of the blood vessels. The top of the skull is removed to collect the dural membranes. The membrane samples are removed from both hemispheres, rinsed with water, and spread flat on microscope slides. The slides are dried for 15 minutes on a slide warmer and cover-slipped with a 70% glycerol/water solution.

A fluorescence microscope (Zeiss) equipped with a grating monochromator and a spectrophotometer are used to quantify the amount of FITC-BSA dye in each dural sample. The microscope is equipped with a motorized stage interfaced with a personal computer. This facilitates the computer-controlled movement of the stage, with

fluorescence measurements at 25 points (500 μm steps) on each dural sample. The extravasation induced by electrical stimulation of the trigeminal ganglion is an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion is stimulated). This allows the other (unstimulated) half of the dura to be used as a control. The extravasation ratio (i.e. the ratio of the amount of extravasation in the dura from the stimulated side compared to the unstimulated side) is calculated.

SEQUENCES

ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNVGSKAF (SEQ ID NO:1)

ACNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF (SEQ ID NO:2)

Antibody	LCDR1	LCDR2	LCDR3
I	RASQDIDNYLN (SEQ ID NO:3)	YTSEYHS (SEQ ID NO:4)	QQGDALPPT (SEQ ID NO:5)
II	RASQDIDNYLN (SEQ ID NO:3)	YTSEYHS (SEQ ID NO:4)	QQGDALPPT (SEQ ID NO:5)
III	RASKDISKYLN (SEQ ID NO:6)	YTSGYHS (SEQ ID NO:7)	QQGDALPPT (SEQ ID NO:5)
IV	RASRPIDKYLN (SEQ ID NO:8)	YTSEYHS (SEQ ID NO:4)	QQGDALPPT (SEQ ID NO:5)
V	RASQDIDKYLN (SEQ ID NO:9)	YTSGYHS (SEQ ID NO:7)	QQGDALPPT (SEQ ID NO:5)
consensus	$RASX_1X_2IX_3X_4YLN$ (SEQ ID NO:10)	$YTSX_5YHS$ (SEQ ID NO:11)	QQGDALPPT (SEQ ID NO:5)

X_1 is Q, R or K;

X_2 is D or P;

X_3 is D or S;

X_4 is N or K; and

X_5 is G or E.

Antibody	HCDR1	HCDR2	HCDR3
I	GYTFGNYWMQ (SEQ ID NO:12)	AIYEGTGDTRYIQKFAG (SEQ ID NO:13)	LSDYVSGFSY (SEQ ID NO:14)
II	GYTFGNYWMQ (SEQ ID NO:12)	AIYEGTGKTVYIQKFAG (SEQ ID NO:15)	LSDYVSGFSY (SEQ ID NO:14)
III	GYTFGNYWMQ (SEQ ID NO:12)	AIYEGTGKTVYIQKFAD (SEQ ID NO:16)	LSDYVSGFGY (SEQ ID NO:39)
IV	GYTFGNYWMQ (SEQ ID NO:12)	AIYEGTGKTVYIQKFAG (SEQ ID NO:15)	LSDYVSGFGY (SEQ ID NO:39)
V	GYTFGNYWMQ (SEQ ID NO:12)	AIYEGTGKTVYIQKFAG (SEQ ID NO:15)	LSDYVSGFGY (SEQ ID NO:39)
consensus	GYTFGNYWMQ (SEQ ID NO:12)	AIYEGTGX_6TX_7YIQKFAX_8 (SEQ ID NO:37)	LSDYVSGFX_9Y (SEQ ID NO:38)

X_6 is K or D;

X_7 is V or R;

X_8 is D or G; and

X_9 is G or S.

DIQMTQSPSSLSASVGDRVTITCRASQDIDNYLNWYQQKPGKAPKLLIYYTSEYH SGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQGDALPPTFGQGTKLEIK (SEQ ID NO: 17)

DIQMTQSPSSLSASVGDRVTITCRASQDIDNYLNWYQQKPGKAPKLLIYYTSEYH SGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQGDALPPTFGQGTKLEIK (SEQ ID NO: 18)

DIQMTQSPSSLSASVGDRVTITCRASKDISKYLNWYQQKPGKAPKLLIYYTSGYH SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDALPPTFGGGTKVEIK (SEQ ID NO: 19)

DIQMTQSPSSLSASVGDRVTITCRASRPIDKYLNWYQQKPGKAPKLLIYYTSEYHS GVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQGDALPPTFGQGTKLEIK (SEQ ID NO: 20)

DIQMTQSPSSLSASVGDRVTITCRASQDIDKYLNWYQQKPGKAPKLLIYYTSGYH SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDALPPTFGGGTKVEIK (SEQ ID NO: 21)

QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI YEGTGDTRYIQKFAGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLSDYVSG FSYWGQGTLVTVSS (SEQ ID NO: 22)

QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI YEGTGKTVYIQKFAGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLSDYVSG FSYWGQGTLVTVSS (SEQ ID NO: 23)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI YEGTGKTVYIQKFADRVTITADKSTSTAYMELSSLRSEDTAVYYCARLSDYVSGF GYWGQGTTVTVSS (SEQ ID NO: 24)

QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI YEGTGKTVYIQKFAGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLSDYVSG FGYWGQGTLVTVSS (SEQ ID NO: 25)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI YEGTGKTVYIQKFAGRVTITADKSTSTAYMELSSLRSEDTAVYYCARLSDYVSGF GYWGQGTTVTVSS (SEQ ID NO: 26)

DIQMTQSPSSLSASVGDRVTITCRASQDIDNYLNWYQQKPGKAPKLLIYYTSEYH SGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQGDALPPTFGQGTKLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 27)

DIQMTQSPSSLSASVGDRVTITCRASQDIDNYLNWYQQKPGKAPKLLIYYTSEYH SGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQGDALPPTFGQGTKLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 28)

DIQMTQSPSSLSASVGDRVTITCRASKDISKYLNWYQQKPGKAPKLLIYYTSGYH SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDALPPTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 29)

DIQMTQSPSSLSASVGDRVTITCRASRPIDKYLNWYQQKPGKAPKLLIYYTSEYHS GVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQGDALPPTFGQGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 30)

DIQMTQSPSSLSASVGDRVTITCRASQDIDKYLNWYQQKPGKAPKLLIYYTSGYH SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDALPPTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 31)

QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI
YEGTGDTRYIQKFAGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLSDYVSG
FSYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN
HYTQKSLSLSLG (SEQ ID NO: 32)

QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI
YEGTGKTVYIQKFAGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLSDYVSG
FSYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN
HYTQKSLSLSLG (SEQ ID NO: 33)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI
YEGTGKTVYIQKFADRVTITADKSTSTAYMELSSLRSEDTAVYYCARLSDYVSGF
GYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR
VESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV
QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLG (SEQ ID NO: 34)

QVQLVQSGAEVKKPGASVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI
YEGTGKTVYIQKFAGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLSDYVSG
FGYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK
RVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVS
NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN
HYTQKSLSLSLG (SEQ ID NO: 35)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI
YEGTGKTVYIQKFAGRVTITADKSTSTAYMELSSLRSEDTAVYYCARLSDYVSGF
GYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR
VESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV
QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLG (SEQ ID NO: 36)

EIVLTQSPATLSLSPGERATLSCKASKRVTTYVSWYQQKPGQAPRLLIYGASNRY
LGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCSQSYNYPYTFGQGTKLEIK (SEQ
ID NO: 40)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWISWVRQAPGKGLEWVAEIRSE
SDASATHYAEAVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCLAYFDYGLAI
QNYWGQGTLVTVSS (SEQ ID NO: 41)

DIQMTQSPSSLSASVGDRVTITCRASX$_1$X$_2$IX$_3$X$_4$YLNWYQQKPGKAPKLLIYYTSX$_5$
YHSGVPSRFSGSGSGTDFTX$_6$TISSLQPEDX$_7$ATYYCQQGDALPPTFGX$_8$GTKX$_9$EIK

X$_1$=Q, K, or R;

X$_2$=D or P;

X_3 D or S;

X_4=K or N;

X_5=E or G;

X_6= F or L;

X_7=I or F;

X_8=Q or G; and

X_9=L or V. (SEQ ID NO: 42)

QVQLVQSGAEVKKPGX$_1$SVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI YEGTGX$_2$TX$_3$YIQKFAX$_4$RVTX$_5$TX$_6$DX$_7$STSTX$_8$YMELSSLRSEDTAVYYCARLSDY VSGFX$_9$YWGQGTX$_{10}$VTVSS

X_1= A or S;

X_2= K or D;

X_3=V or R;

X_4= G or D;

X_5= M or I;

X_6=R or A;

X_7=T or K;

X_8=V or A;

X_9=G or S; and

X_{10}=L or T. (SEQ ID NO: 43)

We claim:

1. A human engineered CGRP antibody comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR comprises LCDR1, LCDR2, LCDR3 amino acid sequences and HCVR comprises HCDR1, HCDR2, HCDR3 amino acid sequences, wherein LCDR1 is SEQ ID NO: 10, LCDR2 is SEQ ID NO: 11, LCDR3 is SEQ ID NO: 5 HCDR1 is SEQ ID NO: 12, HCDR2 is SEQ ID NO: 37and HCDR3 is SEQ ID NO: 38, wherein the human CGRP antibody binds to human CGRP.

2. The human engineered CGRP antibody of claim 1, wherein LCDR1 is RASQDIDNYLN (SEQ ID NO: 3), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGDTRYIQKFAG (SEQ ID NO: 13), and HCDR3 is LSDYVSGFSY (SEQ ID NO: 14).

3. The human engineered CGRP antibody of claim 1, wherein LCDR1 is RASQDIDNYLN (SEQ ID NO: 3), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFSY (SEQ ID NO: 14).

4. The human engineered CGRP antibody of claim 1, wherein LCDR1 is RASKDISKYLN (SEQ ID NO: 6), LCDR2 is YTSGYHS (SEQ ID NO: 7), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAD (SEQ ID NO: 16), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39).

5. The human engineered CGRP antibody of claim 1, wherein LCDR1 is RASRPIDKYLN (SEQ ID NO: 8), LCDR2 is YTSEYHS (SEQ ID NO: 4), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12),

HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39).

6. The human engineered CGRP antibody of claim 1, wherein LCDR1 is RASQDIDKYLN (SEQ ID NO: 9), LCDR2 is YTSGYHS (SEQ ID NO: 7), LCDR3 is QQGDALPPT (SEQ ID NO: 5), HCDR1 is GYTFGNYWMQ (SEQ ID NO: 12), HCDR2 is AIYEGTGKTVYIQKFAG (SEQ ID NO: 15), and HCDR3 is LSDYVSGFGY (SEQ ID NO: 39).

7. The human engineered CGRP antibody of claim 1, wherein the LCVR amino acid sequence is SEQ ID NO: 42 and the HCVR amino acid sequence is SEQ ID NO: 43.

8. The human engineered CGRP antibody of claim 2, wherein said LCVR amino acid sequence is SEQ ID NO: 17 and said HCVR amino acid sequence is SEQ ID NO: 22.

9. The human engineered CGRP antibody of claim 3, wherein said LCVR amino acid sequence is SEQ ID NO: 18 and said HCVR amino acid sequence is SEQ ID NO: 23.

10. The human engineered CGRP antibody of claim 4, wherein said LCVR amino acid sequence is SEQ ID NO: 19 and said HCVR amino acid sequence is SEQ ID NO: 24.

11. The human engineered CGRP antibody of claim 5, wherein said LCVR amino acid sequence is SEQ ID NO: 20 and said HCVR amino acid sequence is SEQ ID NO: 25.

12. The human engineered CGRP antibody of claim 6, wherein said LCVR amino acid sequence is SEQ ID NO: 21 and said HCVR amino acid sequence is SEQ ID NO: 26.

13. The human engineered CGRP antibody of claim 8, wherein said antibody comprises a light chain and a heavy chain, wherein the light chain amino acid sequence is SEQ ID NO: 27 and the heavy chain amino acid sequence is SEQ ID NO: 32.

14. The human engineered CGRP antibody of claim 9, wherein said antibody comprises a light chain and a heavy chain, wherein the light chain amino acid sequence is SEQ ID NO: 28 and the heavy chain amino acid sequence is SEQ ID NO: 33.

15. The human engineered CGRP antibody of claim 10, wherein said antibody comprises a light chain and a heavy chain, wherein the light chain amino acid sequence is SEQ ID NO: 29 and the heavy chain amino acid sequence is SEQ ID NO: 34.

16. The human engineered CGRP antibody of claim 11, wherein said antibody comprises a light chain and a heavy chain, wherein the light chain amino acid sequence is SEQ ID NO: 30 and the heavy chain amino acid sequence is SEQ ID NO: 35.

17. The human engineered CGRP antibody of claim 12, wherein said antibody comprises a light chain and a heavy chain, wherein the light chain amino acid sequence is SEQ ID NO: 31 and the heavy chain amino acid sequence is SEQ ID NO: 36.

18. The human engineered a CGRP antibody of claim 13, wherein said antibody comprises two light chains and two heavy chains, wherein each light chain amino acid sequence is SEQ ID NO: 27 and each heavy chain amino acid sequence is SEQ ID NO: 32.

19. The human engineered CGRP antibody of claim 14, wherein said antibody comprises two light chains and two heavy chains, wherein each light chain amino acid sequence is SEQ ID NO: 28 and each heavy chain amino acid sequence is SEQ ID NO: 33.

20. The human engineered CGRP antibody of claim 15, wherein said antibody comprises two light chains and two heavy chains, wherein each light chain amino acid sequence is SEQ ID NO: 29 and each heavy chain amino acid sequence is SEQ ID NO: 34.

21. The human engineered CGRP antibody of claim 16, wherein said antibody comprises two light chains and two heavy chains, wherein each light chain amino acid sequence is SEQ ID NO: 30 and each heavy chain amino acid sequence is SEQ ID NO: 35.

22. The human engineered CGRP antibody of claim 17, wherein said antibody comprises two light chains and two heavy chains, wherein each light chain amino acid sequence is SEQ ID NO: 31 and each heavy chain amino acid sequence is SEQ ID NO: 36.

23. A pharmaceutical composition, comprising the human engineered CGRP antibody of any one of claims 1-22 and a pharmaceutically acceptable carrier, diluent, or excipient.

24. A method of treating osteoarthritis pain comprising administering to a human patient in need thereof the human engineered CGRP antibody of any one of claims 1-22.

25. A human engineered CGRP antibody thereof as claimed in any one of claims 1-22 for use in therapy.

26. A human engineered CGRP antibody thereof of any one of claims 1-22 for use in the treatment of osteoarthritis pain.

27. The use of a human engineered CGRP antibody of any one of claims 1-22 for use in the manufacture of a medicament for the treatment of osteoarthritis pain.

28. A method of treating migraines comprising administering to a human patient in need thereof the human engineered CGRP antibody of any one of claims 1-22.

29. A human engineered CGRP antibody of any one of claims 1-22 for use in the treatment of migraines.

30. The use of a human engineered CGRP antibody of any one of claims 1-22 for use in the manufacture of a medicament for the treatment of migraines.

31. An antigen-binding fragment of the human engineered CGRP antibody of any one of claims 1-22 or 25-28.