receptor-inhibition (EGFR-I) in the treatment of neuropathic pain. *Br J Anaesth*. 2015; 115(5):761-767). However, targeting the receptor with EGFR antibodies or EGFR tyrosine kinase inhibitors has been found to be associated with high incidence of gastrointestinal (GI) and skin adverse reactions which limit their potential use in chronic pain disorders.

Antibodies which bind to both TGFα and epiregulin are disclosed in WO 2012/138510, along with methods of treatment of diabetic nephropathy. LY3016859 is a monoclonal antibody that binds epiregulin and transforming growth factor α (TGF-α), which was tested in phase 1 clinical studies, and evaluated for safety, pharmacokinetics, pharmacodynamics, and efficacy in healthy subjects and patients with diabetic nephropathy (*See* Sloan-Lancaster, et al., Evaluation of the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy After Single and Multiple Dosings of LY3016859 in Healthy Subjects and Patients With Diabetic Nephropathy, Clinical Pharmacology in Drug Development 2018, 7(7) 759–772). Sloan-Lancaster et al. recites that LY3016859 has greater affinity for TGFα than epiregulin, and further that LY3016859 administration did not result in any obvious effects on nephropathy disease-related biomarkers (See also Beidler, et al., J. Pharmacology and Experimental Therapeutics, 2014, 349(2):330-343). Non-linear kinetics were seen suggesting target mediated drug disposition, and high doses were required for high levels of soluble target engagement. Notably there was a high frequency of anti-LY3016859 antibodies observed in both reported studies, but no clear impact on the pharmacokinetics, or target engagement, as indicated by dose and time dependent increases in circulating epiregulin measured in a drug tolerated assay. For treatment of chronic pain indications, antibodies that are more selective for epiregulin, have higher affinity, and are less likely to induce anti-drug antibody responses, represent an important unmet therapeutic need. There remains an unmet need for alternative and/or improved treatments for chronic pain disorders, including nociceptive, neuropathic, and mixed pain, and in particular in the treatment of osteoarthritis, or diabetic peripheral neuropathy, or chronic low back pain, and/or treatments for therapy resistant pain.

Summary:

In a first aspect of the present disclosure, there is provided an antibody that binds human epiregulin wherein the antibody comprises a heavy chain variable region (VH) and

a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions (HCDR) HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions (LCDR) LCDR1, LCDR2, and LCDR3, wherein

the HCDR1 comprises SEQ ID NO: 5,

the HCDR2 comprises SEQ ID NO: 6,

the HCDR3 comprises SEQ ID NO: 7,

the LCDR1 comprises SEQ ID NO: 8,

the LCDR2 comprises SEQ ID NO: 9, and

the LCDR3 comprises SEQ ID NO: 10.

In another aspect of the present disclosure, there is provided a nucleic acid comprising the sequence of SEQ ID NO: 11 or 12.

In yet another aspect of the present disclosure, there is provided a vector comprising a nucleic acid as disclosed herein.

In a further aspect of the present disclosure, there is provided a composition comprising a first vector comprising a nucleic acid sequence of SEQ ID NO: 11, and a second vector comprising a nucleic acid sequence of SEQ ID NO: 12.

In another aspect of the present disclosure, there is provided a cell comprising the vector as disclosed herein.

In yet another aspect of the present disclosure, there is provided a cell comprising a first vector comprising a nucleic acid sequence of SEQ ID NO: 11, and a second vector comprising a nucleic acid sequence of SEQ ID NO: 12.

In a further aspect of the present disclosure, there is provided a process of producing an antibody comprising culturing the cell as disclosed herein under conditions such that the antibody is expressed and recovering the expressed antibody from the culture medium.

In another aspect of the present disclosure, there is provided an antibody produced by the process as disclosed herein.

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody as disclosed herein, and a pharmaceutically acceptable excipient, diluent or carrier.

In a further aspect of the present disclosure, there is provided a use of an antibody as disclosed herein, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating a pain disorder in a subject in need thereof.

In another aspect of the present disclosure, there is provided an antibody as disclosed herein for use in therapy.

In yet another aspect of the present disclosure, there is provided an antibody as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in the treatment of a pain disorder.

In a further aspect of the present disclosure, there is provided a method of determining the human epiregulin level in a bodily fluid sample comprising:

(a) contacting the bodily fluid sample with an anti-human epiregulin diagnostic monoclonal antibody, or antigen-binding fragment thereof, as disclosed herein, wherein the contacting occurs *ex vivo*;

(b) optionally, removing any non-specifically bound monoclonal antibody or, antigen-binding fragment thereof; and

(c) detecting and/or quantifying the amount of monoclonal antibody, or antigen-binding fragment thereof, which is specifically bound to human epiregulin.

Examples of the present disclosure provide novel anti-human epiregulin antibodies, pharmaceutical compositions thereof, and methods of using these antibodies

and compositions in the treatment of pain and chronic pain disorders. According to some examples, the present disclosure provides antibodies which comprise a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity determining regions (CDRs) LCDR1, LCDR2 and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2 and HCDR3, and are selected from the groupings of CDR combinations provided in Table 1. Sequence identifiers used herein are listed in Table 1, and the sequences are provided in the amino acid and nucleotide sequence listing provided herein. Antibody 1 is a high-affinity fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to residues in the C-terminal regions of human epiregulin and prevents binding of human epiregulin to EGFR and activation of EGFR. Antibody 1 represents an improved anti-epiregulin antibody for human therapy, which possesses a combination of advantageous properties including enhanced affinity, selectivity, decreased risk of off-target and undesirable activities, decreased risk for immunogenicity, high potency and long duration of action, as well as other desirable properties, and provides improved means to block epiregulin and treat pain and chronic pain disorders.

Table 1: Amino Acid and Nucleotide Sequences for Antibody 1

	Antibody 1
SEQ ID HC	1
SEQ ID LC	2
SEQID HCVR	3
SEQID LCVR	4
SEQID HCDR1	5
SEQID HCDR2	6
SEQID HCDR3	7
SEQID LCDR1	8
SEQID LCDR2	9
SEQID LCDR3	10
SEQ ID: DNA HC	11
SEQ ID DNA LC	12

Accordingly, examples of the present disclosure also provide antibodies comprising a LCVR and a HCVR wherein the LCVR has the amino acid sequence of SEQ ID NO: 4 and the HCVR has the amino acid sequence of SEQ ID NO: 3.

According to other examples, the present disclosure also provides antibodies comprising a LCVR and a HCVR wherein the LCVR has the amino acid sequence of SEQ ID NO: 4 and the HCVR has the amino acid sequence of SEQ ID NO: 3, with a hinge region and Fc region selected from SEQ ID NO: 51 and SEQ ID NO: 52.

In some examples, the present disclosure also provides antibodies comprising a LC having the amino acid sequence of SEQ ID NO: 2 and a HC having the amino acid sequence of SEQ ID NO: 1. According to other examples, the present disclosure also provides antibodies comprising a LC and a HC having amino acid sequences with at least 95% homology to the amino acid sequences of the LC having the amino acid sequence of SEQ ID NO: 2 and the HC having the amino acid sequence of SEQ ID NO: 1.

As used herein “Antibody 1” refers to an antibody having the HCDR1 amino acid sequence of SEQ ID NO: 5, the HCDR2 amino acid sequence of SEQ ID NO: 6, the HCDR3 amino acid sequence of SEQ ID NO: 7, the LCDR1 amino acid sequence of SEQ ID NO: 8, the LCDR2 amino acid sequence of SEQ ID NO: 9, the LCDR3 amino acid sequence of SEQ ID NO: 10, the HCVR amino acid sequence of SEQ ID NO: 3, the LCVR amino acid sequence of SEQ ID NO: 4, the HC amino acid sequence of SEQ ID NO: 1, the LC amino acid sequence of SEQ ID NO: 2, or encoded by the HC DNA sequence of SEQ ID NO: 11, or encoded by the LC DNA sequence of SEQ ID NO: 12. The framework and CDR sequences in each of the antibodies for which sequences are set forth herein are annotated using annotation rules in agreement with the method of North, *et al.. J. Mol. Biol. 2011*: 406: 228-256 unless otherwise specified.

The carboxy-terminal portion of each HC defines a constant region primarily responsible for effector functions, and in some examples of the present disclosure the antibodies have one or more modifications in the constant region of each HC that reduce effector functions. Preferably, examples of the present disclosure are IgG4 antibodies, and thus contain an IgG4 Fc region, or an Fc region derived from human IgG4, e.g., a modified IgG4 Fc region.

According to some examples, modifications in the constant region of both HCs which reduce effector functions, and amino acid substitutions are introduced into the IgG4 hinge and Fc regions. Thus, some examples have modifications in the constant region of both HCs which include the amino acid alanine at both residues 229 and 230 (EU Index positions 234-235) (exemplified in HC of Antibody 1, and illustrated in SEQ ID NO: 52), and further modifications in the constant region of both HCs promoting stability, including the amino acid proline at residue 223 (EU Index positions 228) (exemplified in HC of Antibody 1, and illustrated in SEQ ID NO: 51), and the deletion of the amino acid lysine at residue 442 (EU Index positions 447) (exemplified HC of SEQ ID NO: 1).

The antibodies of the present disclosure are believed to have a combination of particularly advantageous properties over prior art anti-epiregulin antibodies, including but not limited to, one or more of the following properties: 1) high binding affinity and desirable association and dissociation rates, 2) potency in neutralization of human epiregulin to achieve a pain mitigating response and *in vivo* efficacy, 3) sufficiently potent as a monotherapy for the treatment and/or prevention of pain disorders; 4) a sustained duration of action; 5) sufficiently limited injection site reactions, 6) acceptably low immunogenicity (i.e., sufficiently non-immunogenic in humans); 7) reduction of untoward skin rash reactions, and/or 8) desirable *in vivo* stability, physical and chemical stability including, but not limited to, thermal stability, solubility, low self-association, and pharmacokinetic characteristics which are acceptable for development and/or use in the treatment of pain disorders, for example chronic pain, including nociceptive, neuropathic, and mixed pain, and in particular in the treatment of chronic osteoarthritis pain, or chronic diabetic peripheral neuropathy pain, or chronic low back pain.

Examples of the present disclosure provide a significant advance over the prior art by providing antibodies against human epiregulin, compositions thereof and methods useful in the treatment, downregulation, or amelioration of pain disorders, through epiregulin neutralization, using a pharmacologically advantageous anti-human epiregulin antibody as provided in the examples described herein. Anti-human epiregulin antibodies of the present disclosure are capable of mitigating pain symptoms, improving pain pathophysiology, preferably, through inhibition of the pain response, particularly in

chronic pain disorders and pain states. The use of such antibodies clinically may lead to extended relief of the pain associated disorder(s) being treated.

Further, there is a need for diagnostic anti-human epiregulin antibodies that are specific for human epiregulin, and possess improved binding affinity, and demonstrate enhanced sensitivity in human epiregulin determinations, and improved enzyme-linked immunosorbent assay (ELISA) assay conditions that result in minimal interference and broad dilutional linearity. According to some examples of the present disclosure, anti-human epiregulin antibodies, including human epiregulin neutralizing antibodies, are provided which bind human epiregulin given by SEQ ID NO: 21. “Epiregulin” or “human epiregulin” refers to human epiregulin protein. As used herein epiregulin refers to the mature epiregulin peptide. Epiregulin (also known as EREG, EPR) is a 46-amino acid protein that belongs to the Epidermal Growth Factor (EGF) family of peptide hormones. Epiregulin is produced as a 162-amino acid transmembrane epiregulin precursor which is cleaved to release the 46-amino acid mature peptide of the following sequence: “VSITKCSSDMNGYCLHGQCIYLVDMSQNYCRCEVGYTGVRCEHFFL” (SEQ ID NO: 21) (see for example Toyoda, et al., Molecular cloning of mouse epiregulin, a novel epidermal growth factor-related protein, expressed in the early stage of development. FEBS Lett. 1995; 377:403–7). Human epiregulin (SEQ ID NO: 22), as described and prepared in Example 2, may for example be used in *in vitro* experiments described herein. References to the ability of the antibodies as described herein to bind and/or to neutralize human epiregulin pertain also to their ability to bind and to neutralize human epiregulin in *in vitro* experiments.

As used herein, “human anti-epiregulin antibody” or “anti-human epiregulin antibody” refers to an antibody that binds to human epiregulin, and when administered *in vitro* or *in vivo*, results in an epiregulin activity-neutralizing and/or blocking response, such as at least one significantly lessened activity. For example, a desired reduction in epiregulin signaling as evidenced by a change in an epiregulin responsive molecular or cellular endpoint(s). As used herein, the terms “signaling” and “signal transduction” and “epiregulin-mediated” as they relate to epiregulin, refer to cellular and/or intercellular responses which result from the activity of epiregulin.

The term “antibody,” as used herein, refers to an immunoglobulin molecule that binds an antigen. Examples of an antibody include a monoclonal antibody, polyclonal

antibody, human antibody, humanized antibody, chimeric antibody, or conjugated antibody. The antibodies can be of any class (e.g., IgG, IgE, IgM, IgD, IgA) and any subclass (e.g., IgG1, IgG2, IgG3, IgG4). An exemplary antibody is an immunoglobulin G (IgG) type antibody comprised of four polypeptide chains: two heavy chains (HC) and two light chains (LC) that are cross-linked via inter-chain disulfide bonds. LCs are classified as kappa or lambda, which are each characterized by a specific constant region. Examples of the present disclosure may comprise an IgG1 or IgG4 antibody, and further comprise kappa light chains or lambda light chains. Preferably antibodies of the present disclosure comprise light chain constant regions which are kappa constant regions.

HCs are classified as gamma, mu, alpha, delta, or epsilon, and define the isotype of an antibody as IgG, IgM, IgA, IgD, or IgE, respectively. The amino-terminal portion of each of the four polypeptide chains includes a variable region of about 100-125 or more amino acids primarily responsible for antigen recognition. The carboxyl-terminal portion of each of the four polypeptide chains contains a constant region primarily responsible for effector functions. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region. The constant region of the heavy chains contains CH1, CH2, and CH3 domains. CH1 comes after the HCVR; the CH1 and HCVR form the heavy chain portion of an antigen-binding (Fab) fragment, which is the part of an antibody that binds antigen(s). CH2 comes after the hinge region and before CH3. CH3 comes after CH2 and is at the carboxy-terminal end of the heavy chain. The constant region of the light chains contains one domain, CL. CL comes after the LCVR; the CL and LCVR form the light chain portion of a Fab.

The antibodies of the present disclosure include IgG HCs which can be further divided into subclasses, e.g., IgG1, IgG2, IgG3, IgG4, and examples of the present disclosure may include one or more modifications in the constant region of each HC, for example that enhance or reduce effector function. The term “Fc region” as used herein refers to a region of an antibody, which comprises the CH2 and CH3 domains of the antibody heavy chain. Optionally, the Fc region may include a portion of the hinge region or the entire hinge region of the antibody heavy chain. IgG1 is known to induce antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), and Fc mutations described herein may reduce aggregation, reduce, or enhance ADCC or CDC activities (or other functions), and/or modify the pharmacokinetics of the antibodies.

Examples of anti-human EREG antibodies described herein have reduced binding to the FcγR and C1q receptors, thereby reducing or eliminating the cytotoxicity which may be induced by antibodies with wild type IgG Fc regions. Thus, according to some examples, mutations are introduced in the Fc region at positions as described herein. Patient safety can be improved with sufficiently reduced or eliminated effector functions of such anti-human EREG antibodies comprising a modified Fc region, and in combination with other properties described herein, provide therapeutic agents with an improved profile of useful activities while avoiding undesirable activities.

When expressed in certain biological systems, antibodies are glycosylated in the Fc region. Typically, glycosylation occurs in the Fc region of the antibody at a highly conserved N-glycosylation site. N-glycans typically attach to asparagine. Antibodies may be glycosylated at other positions as well. Antibodies of the present disclosure are monoclonal antibodies. Monoclonal antibodies are antibodies derived from a single copy or clone including, for example, any eukaryotic, prokaryotic or phage clone, and not defined by the method by which it is produced. Monoclonal antibodies can be produced, for example, by hybridoma technologies, recombinant technologies, phage display technologies, synthetic technologies, e.g., CDR-grafting, or combinations of such or other technologies known in the art. The present disclosure contemplates the antibodies of the present disclosure are human or humanized antibodies. In the context of monoclonal antibodies, the terms “human” and “humanized” are well-known to those of ordinary skill in the art (Weiner LJ, J. Immunother. 2006; 29: 1-9; Mallbris L, et al., J. Clin. Aesthet. Dermatol. 2016; 9: 13-15). Exemplary examples of antibodies of the present disclosure also include antibody fragments or antigen-binding fragments, which comprise at least a portion of an antibody retaining the ability to specifically interact with an antigen such as Fab, Fab’, F(ab’)2, Fv fragments, scFv antibody fragments, disulfide-linked Fvs (sdFv), a Fd fragment and linear antibodies.

The amino terminal portion of each LC and HC includes a variable region of about 100-120 amino acids primarily responsible for antigen recognition via the CDRs contained therein. The VH and VL regions can be further subdivided into regions of hyper-variability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). The CDRs are exposed on the surface of the protein and are important regions of the antibody for antigen binding

Table 2:

Exemplary CDRs of Antibody 1 (or Antibodies of the present disclosure)						
Ab	**HCDR1**	**HCDR2**	**HCDR3**	**LCDR1**	**LCDR2**	**LCDR3**
North	TVSGGSISSYYWS (SEQ ID NO: 5)	RIYPSGNTN (SEQ ID NO: 6)	ARGGLVMDV (SEQ ID NO: 7)	RASQSVEFSYLA (SEQ ID NO: 8)	YGASSRAT (SEQ ID NO: 9)	HQYGTNPFT (SEQ ID NO: 10)
Kabat	SYYWS (SEQ ID NO: 31)	RIYPSGNTNYNPSLKS (SEQ ID NO: 32)	GGLVMDV (SEQ ID NO: 33)	RASQSVEFSYLA (SEQ ID NO: 34)	GASSRAT (SEQ ID NO: 35)	HQYGTNPFT (SEQ ID NO: 36)
Chothia	GGSISSY (SEQ ID NO: 37)	YPSGN (SEQ ID NO: 38)	GGLVMDV (SEQ ID NO: 39)	RASQSVEFSYLA (SEQ ID NO: 40)	GASSRAT (SEQ ID NO: 41)	HQYGTNPFT (SEQ ID NO: 42)
IMGT	GGSISSYY (SEQ ID NO: 43)	IYPSGNT (SEQ ID NO: 44)	ARGGLVMDV (SEQ ID NO: 45)	QSVEFSY (SEQ ID NO: 46)	GAS (SEQ ID NO: 47)	HQYGTNPFT (SEQ ID NO: 48)

Antibody examples of the present disclosure possess a combination of several pharmacologically useful and important activities, and in one respect are capable of binding with high affinity to human epiregulin, and high specificity for human epiregulin, as well as other useful properties. The terms “bind” and “binds” as used herein are intended to mean, unless indicated otherwise, the ability of a protein or molecule to form attractive interactions with another protein or molecule, which result in proximity of the two proteins or molecules as determined by common methods known in the art. The phrase “specifically binds”, as used herein in, refers to the affinity of an anti-epiregulin antibody for human epiregulin, and is intended to mean, unless indicated otherwise, a K_D of less than about 2×10^{-9} M, and preferably less than about 2×10^{-11} M, and even more preferably, between about 2×10^{-11} M and about 2×10^{-12} M, as determined at about pH 7.4, by common methods known in the art, including use of MSD-SET (solution equilibrium titration) as described herein. The phrase “specifically binds” also indicates the relative affinity of an anti-epiregulin antibody for human epiregulin, as compared to

other antigens, and in particular the EGFR-ligand TGFα, wherein the affinity for human epiregulin results in a specific recognition of human epiregulin and a lack of binding to other EGFR ligands tested.

Antibody examples of the present disclosure may be expressed and produced by a variety of techniques known in the art from constructs comprising sequences of the present examples. The terms “nucleic acid” or “polynucleotide” as used interchangeably herein, refer to polymers of nucleotides, including single-stranded and/or double-stranded nucleotide-containing molecules, such as DNA, cDNA and RNA molecules, incorporating native, modified, and/or analogs of, nucleotides. Polynucleotides of the present disclosure may also include substrates incorporated therein, for example, by DNA or RNA polymerase or a synthetic reaction. A DNA molecule of the present disclosure is a DNA molecule that comprises a non-naturally occurring polynucleotide sequence encoding a polypeptide having the amino acid sequence of at least one of the polypeptides in an antibody of the present disclosure (e.g., heavy chain, light chain, variable heavy chain, and variable light chain).

An isolated DNA encoding a HCVR or LCVR region can be converted to a full-length heavy chain gene by operably linking the respective HCVR or LCVR-encoding DNA to another DNA molecule encoding heavy or light chain constant regions to form a heavy or light chain respectively. The sequences of human, as well as other mammalian, heavy chain constant region genes are known in the art. DNA fragments encompassing these regions can be obtained, *e.g.*, by standard PCR amplification.

The polynucleotides of the present disclosure can be expressed in a host cell after the sequences have been operably linked to an expression control sequence. The expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly expression vectors will contain selection markers, e.g., tetracycline, neomycin, and dihydrofolate reductase, to permit detection of those cells transformed with the desired DNA sequences. The vectors containing the polynucleotide sequences of interest (e.g., the polynucleotides encoding the polypeptides of the antibody and expression control sequences) can be transferred into the host cell by well-known methods which vary depending on the type of cellular host.

The antibodies of the present disclosure can readily be produced in mammalian cells, of which non-limiting examples include CHO, NS0, HEK293 or COS cells. The

We Claim:

1. An antibody that binds human epiregulin wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions (HCDR) HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions (LCDR) LCDR1, LCDR2, and LCDR3, wherein

the HCDR1 comprises SEQ ID NO: 5,
the HCDR2 comprises SEQ ID NO: 6,
the HCDR3 comprises SEQ ID NO: 7,
the LCDR1 comprises SEQ ID NO: 8,
the LCDR2 comprises SEQ ID NO: 9, and
the LCDR3 comprises SEQ ID NO: 10.

2. The antibody of claim 1, wherein the VH comprises SEQ ID NO: 3 and the VL comprises SEQ ID NO: 4.

3. The antibody of claim 1 or 2, wherein the antibody comprises a heavy chain (HC) comprising SEQ ID NO: 1 and a light chain (LC) comprising SEQ ID NO: 2.

4. A nucleic acid comprising the sequence of SEQ ID NO: 11 or 12.

5. A vector comprising a nucleic acid of claim 4.

6. The vector of claim 5, wherein the vector comprises a first nucleic acid sequence of SEQ ID NO: 11 and a second nucleic acid sequence of SEQ ID NO: 12.

7. A composition comprising a first vector comprising a nucleic acid sequence of SEQ ID NO: 11, and a second vector comprising a nucleic acid sequence of SEQ ID NO: 12.

8. A cell comprising the vector of claim 5 or 6.

9. A cell comprising a first vector comprising a nucleic acid sequence of SEQ ID NO: 11, and a second vector comprising a nucleic acid sequence of SEQ ID NO: 12.

10. The cell of claim 8 or 9, wherein the cell is a mammalian cell.

11. A process of producing an antibody comprising culturing the cell of any one of claims 8-10 under conditions such that the antibody is expressed and recovering the expressed antibody from the culture medium.

12. An antibody produced by the process of claim 11.

13. A pharmaceutical composition comprising the antibody of any one of claims 1-3 or 12, and a pharmaceutically acceptable excipient, diluent or carrier.

14. Use of an antibody of any one of claims 1-3 or 12, or the pharmaceutical composition of claim 13, in the manufacture of a medicament for treating a pain disorder in a subject in need thereof.

15. The use of claim 14, wherein the pain disorder is selected from the group consisting of osteoarthritis pain, diabetic peripheral neuropathy pain, and chronic low back pain.

16. The use of claim 15, wherein the pain disorder is osteoarthritis pain.

17. The use of claim 15, wherein the pain disorder is diabetic peripheral neuropathy pain.

18. The use of claim 15, wherein the pain disorder is chronic low back pain.

19. The use of claim 15, wherein the pain disorder is therapy resistant.

20. The antibody of any one of claims 1-3 or 12 for use in therapy.

21. The antibody of any one of claims 1-3 or 12, or the pharmaceutical composition of claim 13, for use in the treatment of a pain disorder.

22. The antibody or pharmaceutical composition for use of claim 21, wherein the pain disorder is selected from the group consisting of osteoarthritis pain, diabetic peripheral neuropathy pain, and chronic low back pain.

23. The antibody or pharmaceutical composition for use of claim 21, wherein the pain disorder is osteoarthritis pain.

24. The antibody or pharmaceutical composition for use of claim 21, wherein the pain disorder is diabetic peripheral neuropathy pain.

25. The antibody or pharmaceutical composition for use of claim 21, wherein the pain disorder is chronic low back pain.

26. A method of determining the human epiregulin level in a bodily fluid sample comprising:

(a) contacting the bodily fluid sample with an anti-human epiregulin diagnostic monoclonal antibody, or antigen-binding fragment thereof, of any one of claims 1-3, wherein the contacting occurs *ex vivo*;

(b) optionally, removing any non-specifically bound monoclonal antibody or, antigen-binding fragment thereof; and

(c) detecting and/or quantifying the amount of monoclonal antibody, or antigen-binding fragment thereof, which is specifically bound to human epiregulin.

27. The method of claim 26, wherein said bodily fluid sample is a blood, serum or plasma sample, or cerebrospinal fluid sample.