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(54) **Title**: SIGLEC 15 ANTIBODIES IN TREATING BONE LOSS-RELATED DISEASE

(57) **Abstract**: Novel antibodies and antigen binding fragments that specifically binds to Siglec-15 are described herein In some embodiments, the antibodies or antigen binding fragments may block the biological activity of Siglec-15 and are useful in composition for the treatment of bone loss, more particularly in bone diseases that have increased cell surface expression of Siglec-15, such as conditions where there is an increase in the bone degradative activity of osteoclasts The invention also relates to cells expressing the antibodies or antigen binding fragments such as monoclonal, humanized or chimeric antibodies Additionally, methods of detecting and treating bone loss, bone-related diseases or cancer using the antibodies and fragments are also disclosed.

SIGLEC 15 ANTIBODIES IN TREATING BONE LOSS-RELATED DISEASE

FIELD OF THE INVENTION

The present invention relates to monoclonal antibodies and antigen binding fragments thereof that specifically bind to Siglec-15 and their use for treating certain diseases including diagnosing, preventing and treating cancer or bone loss, such as severe or excessive bone loss associated with bone-related diseases or associated with an increase in osteoclast differentiation or activity. The present invention also relates to the use of these antibodies for diagnosis, prevention and treatment of various other types of diseases where the activity of osteoclasts is increased.

BACKGROUND OF THE INVENTION

Bone is a dynamic connective tissue comprised of functionally distinct cell populations required to support the structural, mechanical and biochemical integrity of bone and the human body's mineral homeostasis. The principal cell types involved include, osteoblasts responsible for bone formation and maintaining bone mass, and osteoclasts responsible for bone resorption. Osteoblasts and osteoclasts function in a dynamic process termed bone remodelling. The development and proliferation of these cells from their progenitors is governed by networks of growth factors and cytokines produced in the bone microenvironment as well as by systemic hormones. Bone remodelling is ongoing throughout the lifetime of the individual and is necessary for the maintenance of healthy bone tissue and mineral homeostasis. The process remains largely in equilibrium and is governed by a complex interplay of systemic hormones, peptides and downstream signalling pathway proteins, local transcription factors, cytokines, growth factors and matrix remodelling genes.

Any interference or imbalance arising in the bone remodelling process can produce skeletal disease, with the most common skeletal disorders characterized by a net decrease in bone mass. A primary cause of this reduction in bone mass is an increase in osteoclast number and/or activity. The most common of such disease, and perhaps the best known, is osteoporosis occurring particularly in women after the onset of menopause. In fact osteoporosis is the most significant underlying cause of skeletal fractures in late middle-aged and elderly women. While estrogen deficiency has been strongly implicated as a factor in postmenopausal osteoporosis,

there is longstanding evidence that remodelling is a locally controlled process being that it takes place in discrete packets throughout the skeleton as first described by Frost over forty years ago (Frost H.M. 1964).

Since bone remodelling takes place in discrete packets, locally produced hormones and enzymes may be more important than systemic hormones for the initiation of bone resorption and the normal remodelling process. Such local control is mediated by osteoblasts and osteoclasts in the microenvironment in which they operate. For example, osteoclasts attach to the bone matrix and form a separate compartment between themselves and the bone surface delimited by a sealing zone formed by a ring of actin surrounding the ruffled border. Multiple small vesicles transport enzymes toward the bone matrix and internalize partially digested bone matrix. The microenvironment within the sealing zone is rich with the presence of lysosomal enzymes and is highly acidic compared to the normal physiological pH of the body. The ruffled border membrane also expresses RANK, the receptor for RANKL, and macrophage-colony stimulating factor (M-CSF) receptor, both of which are responsible for osteoclast differentiation, as well as the calcitonin receptor capable of rapidly inactivating the osteoclast (Baron, R. 2003).

In a complex pattern of inhibition and stimulation, growth hormone, insulin-like growth factor-1, the sex steroids, thyroid hormone, calciotrophic hormones such as PTH and prostaglandin E2, various cytokines, such as interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha, and 1,25-dihydroxyvitamin D (calcitriol) act co-ordinately in the bone remodelling process (Jilka et al. 1992; Poli et al. 1994; Srivastava et al. 1998; de Vemejoul 1996).

Thus, it stands to reason that the unique local environments created by these specialized cells is due to the expression of either unique genetic sequences not expressed in other tissues and/or splice variants of polynucleotides and polypeptides expressed in other tissues. The isolation and identification of polynucleotides, polypeptides and their variants and derivatives specific to osteoclast activity will permit a clearer understanding of the remodelling process and offer tissue specific therapeutic targets for the treatment of disease states related to bone remodelling.

Many diseases linked to bone remodelling are poorly understood, generally untreatable or treatable only to a limited extent. For example, osteoarthritis is difficult to treat as there is no cure and treatment focuses on relieving pain and preventing

the affected joint from becoming deformed. Non-steroidal anti-inflammatory drugs (NSAIDs) are generally used to relieve pain.

Another example is osteoporosis where the only current medications approved by the FDA for use in the United States are the anti-resorptive agents that prevent bone breakdown. Estrogen replacement therapy is one example of an anti-resorptive agent. Others include alendronate (Fosamax- a biphosphonate anti-resorptive), risedronate (Actonel- a bisphosphonate anti-resorptive), raloxifene (Evista- selective estrogen receptor modulator (SERM)), calcitonin (Calcimar- a hormone), and parathyroid hormone/teriparatide (Forteo- a synthetic version of the human hormone, parathyroid hormone, which helps to regulate calcium metabolism).

Bisphosphonates such as alendronate and risedronate bind permanently to the surface of bone and interfere with osteoclast activity. This allows the osteoblasts to outpace the rate of resorption. The most common side effects are nausea, abdominal pain and loose bowel movements. However, alendronate is reported to also cause irritation and inflammation of the esophagus, and in some cases, ulcers of the esophagus. Risedronate is chemically different from alendronate and has less likelihood of causing esophagus irritation. However, certain foods, calcium, iron supplements, vitamins and minerals, or antacids containing calcium, magnesium, or aluminum can reduce the absorption of risedronate, thereby resulting in loss of effectiveness.

The most common side effect of Raloxifen and other SERMS (such as Tamoxifen) are hot flashes. However, Raloxifene and other hormone replacement therapies have been shown to increase the risk of blood clots, including deep vein thrombosis and pulmonary embolism, cardiovascular disease and cancer.

Calcitonin is not as effective in increasing bone density and strengthening bone as estrogen and the other anti-resorptive agents. Common side effects of either injected or nasal spray calcitonin are nausea and flushing. Patients can develop nasal irritations, a runny nose, or nosebleeds. Injectable calcitonin can cause local skin redness at the site of injection, skin rash, and flushing.

A situation demonstrative of the link between several disorders or disease states involving bone remodelling is that of the use of etidronate (Didronel) first approved by the FDA to treat Paget's disease. Paget's disease is a bone disease characterized by a disorderly and accelerated remodelling of the bone, leading to bone weakness and pain. Didronel has been used 'off-label' and in some studies

shown to increase bone density in postmenopausal women with established osteoporosis. It has also been found effective in preventing bone loss in patients requiring long-term steroid medications (such as Prednisone or Cortisone). However, high dose or continuous use of Didronel can cause another bone disease called osteomalacia. Like osteoporosis, osteomalacia can lead to weak bones with increased risk of fractures. Because of osteomalacia concerns and lack of enough studies yet regarding reduction in the rate of bone fractures, the United States FDA has not approved Didronel for the treatment of osteoporosis.

Osteoporosis therapy has been largely focused on antiresorptive drugs that reduce the rate of bone loss but emerging therapies show promise in increasing bone mineral density instead of merely maintaining it or slowing its deterioration. The osteoporosis early stage pipeline consists largely of drug candidates in new therapeutic classes, in particular cathepsin K inhibitors, osteoprotegerin and calcilytics as well as novel bisphosphonates. Some of these are examples where novel drugs exploiting genomics programs are being developed based on a deeper understanding of bone biology and have the potential to change the face of treatment of bone disorders in the long term.

The present invention describes the use of antibodies specific for Siglec-15 for the diagnosis, prognosis, and treatment (including prevention) of cancer or bone loss (e.g., severe or excessive bone loss associated with bone-related disease or associated with an increase in osteoclast differentiation or activity). In particular, the present invention relates to the use of anti-Siglec-15 antibodies for inhibiting the differentiation of osteoclasts.

Sialic-acid-binding immunoglobulin-like lectins (Siglecs) are members of the immunoglobulin (Ig) superfamily that have the ability to interact with sialic acids (McMillan and Crocker, 2008; Crocker *et al.*, 2007). There are several Siglec family members that all share specific structural features, in particular, displaying an amino-terminal V-set Ig domain that binds to sialic acid and a variable number of C2-set Ig domains. These membrane receptors are generally expressed in highly specific manners and many of the family members are expressed in hematopoietic cells (McMillan and Crocker, 2008). These proteins are thought to promote cell-cell interactions, mediate signalling, and regulate immune functions through the recognition of glycans (Crocker *et al.*, 2007). Sialic acids are nine-carbon sugars typically located at the ends of complex glycoconjugates on the surface of cells. They

can be attached to a wide variety of proteins and lipids (McMillan and Crocker, 2008).

Siglec-15 is one of the most recently described Siglec family members that have a high homology to Siglec-14 (Angata et al., 2007). These authors reported that it preferentially binds to sialyl Tn structure and that it interacts with DAP12 and DAP10. The functional significance of these interactions is not known but it was proposed that Siglec-15 probably harbors an activating function (Angata et al., 2007). Despite these preliminary insights into a potential role in mammals of Siglec-15, important advances in the understanding of the biological function of the protein were contributed when the sequence was identified as part of a screen to discover novel regulators of osteoclast differentiation (Sooknanan et al. 2007). In this patent application, it was revealed that attenuation of the *Siglec-15* transcript by RNA interference in a mouse model of osteoclastogenesis resulted in significant reduction of differentiation of precursors in response to RANKL treatment. Similar results were disclosed in human osteoclasts. Furthermore, the studies presented in this disclosure also showed that the localization of Siglec-15 at the cell membrane was necessary for its function in osteoclast differentiation. Furthermore, a recent publication showed that the presence of sialic acid at the end of surface glycoconjugates was required for proper osteoclast differentiation and were probably important for the fusion of osteoclast precursor cells (Takahata *et al.*, 2007). This last observation creates a direct functional link between sialic acid binding and the expression of Siglec-15 in differentiating osteoclasts and strongly suggested that Siglec-15 plays a role in the early differentiation program of osteoclast precursors.

Thus, the expression profile of Siglec-15, its strong inducibility during osteoclast differentiation, its localization at the surface of the membrane, and its structural features all contribute to the feasibility of targeting this protein at the cell surface with monoclonal antibodies. The only other example of monoclonal antibody-based therapy that target osteoclasts is denosumab, a human monoclonal antibody that is specific for RANKL (Ellis et al. 2008). The present invention relates to the use of anti-Siglec-15 antibodies or antigen binding fragments as blockers of osteoclast differentiation in the detection or treatment of bone loss, especially in the context of bone-related diseases or in the context of increased osteoclast differentiation or activity. The present invention also relates to the use of antibodies or antigen binding fragments in the detection or treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the PCR-based expression profiling of the Siglec-15 mRNA in human differentiating osteoclast samples from six different donors. Also depicted is the expression profiling in RNA samples from 30 human normal tissues. As controls, the Siglec-15 expression pattern was compared to a well-known osteoclast marker, cathepsin K (CATK) and the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was included to control for the quantity of RNA in each sample.

Figure 2 shows the expression of the Siglec-15 mRNA in samples isolated from the NCI-60 panel of cancer cell lines.

Figure 3 presents a Coomassie-stained polyacrylamide gel containing a sample of the purified human recombinant Siglec-15 that was expressed as a Fc fusion protein in 293-6E cells. This preparation was used to generate the monoclonal antibodies disclosed in this patent.

Figure 4 shows the results of an Fc-Siglec-15 ELISA of the individual monoclonal antibodies selected from the 96-well plate from Omniclonal library #25 containing anti-Siglec-15 Fabs. The wells indicated by bold numbers contained the exemplary monoclonals 25A1, 25B4, 25B8, 25C1, 25D8, 25E5, 25E6, and 25E9. Also shown is an ELISA on the same plate using the Fc moiety alone to identify those monoclonals that were specific for the Fc portion of the Fc-Siglec-15 fusion protein.

Figure 5 presents a scheme that illustrates the steps involved to convert the mouse Fabs into IgG2 mouse-human chimeric mAbs.

Figure 6 shows drawings that compare the binding of the mouse anti-Siglec-15 Fabs with the binding of the corresponding IgG2 chimeric monoclonal antibodies for exemplary antibodies 25B4, 25B8, 25C1, 25D8, 25E6, and 25E9. The results indicate that the relative binding of the Fab variable regions was maintained when transferred to a full human IgG2 scaffold.

Figure 7 shows the inhibition of the differentiation of human osteoclasts upon treatment with increasing concentrations of anti-Siglec-15 IgG2 chimeric monoclonal antibodies 25B8, 25E6, and 25E9. After treatment, the osteoclasts were stained for TRAP expression.

Figure 8 shows the inhibition of the differentiation of mouse osteoclasts upon treatment with increasing concentrations of anti-Siglec-15 IgG2 chimeric monoclonal antibodies 25B8, 25E6, and 25D8. After treatment, the osteoclasts were stained for TRAP expression.

Figure 9 shows the comparative binding of the human and mouse Siglec-15 in the presence of the exemplary antibody 25C8. The result indicates that the binding of the antibodies generated against the human Siglec-15 also interact with the mouse Siglec-15.

Figure 10A, **10B** and **10C** is a summary of alignment results obtained for selected CDRL1, CDRL2 and CDRL3 sequences (respectively) using the ClustalW2 program; where " * " means that the residues in that column are identical in all sequences in the alignment, " : " means that conserved substitutions have been observed and " . " means that semi-conserved substitutions are observed. Consensus CDRs were generated using the ClustalW program (Larkin M.A., et al., (2007) ClustalW and ClustalX version 2. *Bioinformatics 2007 23(21): 2947-2948*).

Figure 11A, **11B** and **11C** is a summary of alignment results obtained for selected CDRH1, CDRH2 and CDRH3 sequences (respectively) using the ClustalW2 program; where " * " means that the residues in that column are identical in all sequences in the alignment, " : " means that conserved substitutions have been observed and " . " means that semi-conserved substitutions are observed. Consensus CDRs were generated using the ClustalW program (Larkin M.A., et al., (2007) ClustalW and ClustalX version 2. *Bioinformatics 2007 23(21): 2947-2948*).

Figure 12 illustrates the ability of the 25E9 candidate antibody that is specific for Siglec-15 to inhibit the bone resorbing activity of osteoclasts.

Figure 13A, 13B, 13C, 13D and 13E demonstrate that the Siglec-15 antibodies can detect the protein by immunoblotting of lysates prepared from cells overexpressing the Siglec-15 cDNA (13A), in human (13B) and mouse (13C) osteoclasts, and in U87 glioblastoma cells, and by flow cytometry of intact U87 cells.

Figure 14A and **14B** shows that the antibodies generated against Siglec-15 do not bind other related Siglecs including Siglec-2 and CD33.

Figure 15 shows an ELISA that demonstrates that the anti-Siglec-15 antibodies can inhibit the interaction between Siglec-15 and sialic acids.

SUMMARY OF THE INVENTION

This invention relates to antibodies and antigen binding fragments as well as kits useful for the treatment (including prevention), detection and diagnosis of bone loss or cancer. The antibodies and antigen binding fragments may more particularly be useful for detection of differentiated osteoclast, ovarian cancer cells, renal cancer cells, cancer cells of the central nervous system, prostate cancer cells, melanoma cells, breast cancer cells, lung cancer cells or colon cancer cells and diagnosis of bone loss, ovarian cancer, renal cancer, cancer of the central nervous system, prostate cancer, melanoma, breast cancer, lung cancer or colon cancer. The antibodies or antigen binding fragment of the present invention may also be useful for treating bone loss, ovarian cancer, renal cancer, cancer of the central nervous system, prostate cancer, melanoma, breast cancer, lung cancer or colon cancer.

The antibodies or antigen-binding fragment of the present invention may bind to amino acids 20 to 259 of Siglec-15 (SEQ ID NO.:2) or to a corresponding region of Siglec-15 variant (e.g., SEQ ID NO.:4). More particularly the antibodies or antigen-binding fragment of the present invention may bind to amino acids 49 to 165 of Siglec-15 (SEQ ID NO.:2) or to a corresponding region of a Siglec-15 variant (e.g., SEQ ID NO.:4).

The present invention more particularly relates to an isolated antibody or antigen binding fragment capable of binding to a polypeptide able to promote osteoclast differentiation and of inhibiting an osteoclast differentiation activity of the polypeptide.

The antibodies or antigen binding fragments of the present invention encompass those which bind to amino acids 20 to 259 of SEQ ID NO.:2 or to a variant having at least 80% sequence identity with amino acids 20 to 259 of SEQ ID NO.:2.

More particularly, the antibody or antigen binding fragment of the present invention may more particularly bind to amino acids 49 to 165 of SEQ ID NO.:2 or to a variant having at least 80% sequence identity with amino acids 49 to 165 of SEQ ID NO.:2.

More specifically, antibody or antigen binding fragment of the present invention may more particularly bind to a polypeptide having at least 80% sequence identity with SEQ ID NO.:2.

In accordance with the present invention, the antibody or antigen binding fragment may therefore interfere with the ability of the polypeptide to promote osteoclast differentiation or to promote tumor growth.

An antibody or antigen binding fragment capable of binding to the extracellular region of SEQ ID NO.:2 or the SEQ ID NO.:2 variant is more specifically contemplated.

The present invention therefore provides an isolated antibody or antigen binding fragment capable of binding to a polypeptide able to promote osteoclast differentiation and having at least 80% sequence identity with sEQ ID NO.:2 or with amino acids 20 to 259 of SEQ ID NO.:2 (or at least 80% identity with amino acids 49-165 of SEQ ID NO.:2) of Sialic-acid-binding immunoglobulin-like lectin 15 (Siglec-15; SEQ ID NO.:2), wherein said antibody or antigen binging fragment is capable of inhibiting osteoclast differentiation, bone resorption (degradation) or is capable of blocking Siglec-15 from binding to a sialic acid.

The antibody or antigen binding fragment of the present invention may be capable of interfering with (inhibiting) differentiation of an osteoclast precursor cell into a differentiated osteoclast.

In accordance with the present invention, the isolated antibody or antigen binding fragment may be, for example, a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a human antibody or a fragment thereof.

In an exemplary embodiment, the isolated antibody or antigen binding fragment may be chimeric antibody or a human antibody which may comprise amino acids of a constant region of a human antibody or a fragment thereof.

The constant region or fragment thereof may be from an IgG1, IgG2, IgG3, or IgG4. In a more specific embodiment, the constant region may be from an IgG2.

Antigen binding fragments which may be particularly be useful include, for example, a FV (scFv), a Fab, a Fab' or a $(Fab')_2$.

The antibody or antigen binding fragment may be produced in or from an isolated mammalian cell (other than an hybridoma cell) or in an hybridoma cell. An exemplary embodiment of an isolated mammalian cell is a human cell.

Production of a monoclonal antibody, a chimeric antibody, a human antibody or a fragment thereof in an isolated mammalian cell (e.g., human cell) is particularly contemplated. The chimeric antibody or a human antibody thus produced may comprise amino acids of a constant region of a human antibody or a fragment

thereof, including, for example, a constant region or fragment thereof from an IgG1, IgG2, IgG3, or IgG4. In a more specific embodiment, the constant region may be from an IgG2.

In an aspect of the invention, the antibody or antigen binding fragment of the present invention may interfere (inhibit) with the differentiation of a human osteoclast precursor cell into a differentiated human osteoclast.

In an exemplary embodiment, the antibody or antigen binding fragment of the present invention may interfere (inhibit) with the differentiation of a primary human osteoclast precursor cell into a differentiated human osteoclast.

Antibodies or antigen binding fragments having such activity may include, for example, a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a human antibody or a fragment thereof.

In a more specific embodiment, antibodies or antigen binding fragments that may be capable of having such activity include, for example, a monoclonal antibody, a chimeric antibody, a human antibody or a fragment thereof.

In an even more specific embodiment, antibodies or antigen binding fragments that may be capable of having such activity include, for example, a chimeric antibody, a human antibody or a fragment thereof that may comprise amino acids of a constant region of a human antibody or a fragment thereof.

The constant region or fragment thereof of the chimeric or human antibody may be from an IgG1, IgG2, IgG3, or IgG4. More particularly, the constant region may be from an IgG2.

The antibodies and antigen binding fragments of the present invention may also be used to generally target cells expressing or overexpressing Siglec-15, including bone cells and breast, colon, lung, ovarian, prostate, and renal cancer cells as well as melanoma cells and cancer cells of the central nervous system.

More particularly, the antibodies and antigen binding fragments may be used to target osteoclasts cells undergoing differentiation.

The present invention provides in one aspect thereof, an isolated or substantially purified antibody or antigen binding fragment which may be capable of specific binding to SEQ ID NO:2.

More specifically and in accordance with an embodiment of the invention, the antibody or antigen binding fragment may bind to a domain located between amino acid 20 and amino acid 259 of SEQ ID NO:2.

In accordance with another embodiment of the invention, the antibody or antigen binding fragment may be capable of binding to an epitope comprised within amino acid 20 and amino acid 259 of SEQ ID NO:2.

As such, the present invention encompasses diagnostic and/or therapeutic antibodies or antigen binding fragments having specificity for SEQ ID NO:2. Also encompassed by the present invention are antibodies or antigen binding fragments having the same epitope specificity as the antibody of the present invention. A candidate antibody may be identified by determining whether it will bind to the epitope to which the antibodies described herein binds and/or by performing competition assays with antibodies or antigen binding fragments known to bind to the epitope.

Therefore, another aspect the present invention provides an isolated antibody or antigen binding fragment capable of competing with the antibody or antigen binding fragment described herein.

In further aspects, the present invention provides method of treatment and method of detection using the antibody or antigen binding fragment of the present invention.

The term “antibody” refers to intact antibody, monoclonal or polyclonal antibodies. The term “antibody” also encompasses, multispecific antibodies such as bispecific antibodies. Human antibodies are usually made of two light chains and two heavy chains each comprising variable regions and constant regions. The light chain variable region comprises 3 CDRs, identified herein as CDRL1, CDRL2 and CDRL3 flanked by framework regions. The heavy chain variable region comprises 3 CDRs, identified herein as CDRH1, CDRH2 and CDRH3 flanked by framework regions.

The term "antigen-binding fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to bind to an antigen (e.g., SEQ ID NO:2 or variants thereof). It has been shown that the antigen-binding function of an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term "antigen-binding fragment" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a V_H domain; and (vi) an isolated

complementarity determining region (CDR), e.g., V_H CDR3. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single polypeptide chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding fragment" of an antibody. Furthermore, the antigen-binding fragments include binding-domain immunoglobulin fusion proteins comprising (i) a binding domain polypeptide (such as a heavy chain variable region, a light chain variable region, or a heavy chain variable region fused to a light chain variable region via a linker peptide) that is fused to an immunoglobulin hinge region polypeptide, (ii) an immunoglobulin heavy chain CH2 constant region fused to the hinge region, and (iii) an immunoglobulin heavy chain CH3 constant region fused to the CH2 constant region. The hinge region may be modified by replacing one or more cysteine residues with serine residues so as to prevent dimerization. Such binding-domain immunoglobulin fusion proteins are further disclosed in US 2003/0118592 and US 2003/0133939. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

A typical antigen binding site is comprised of the variable regions formed by the pairing of a light chain immunoglobulin and a heavy chain immunoglobulin. The structure of the antibody variable regions is very consistent and exhibits very similar structures. These variable regions are typically comprised of relatively homologous framework regions (FR) interspaced with three hypervariable regions termed Complementarity Determining Regions (CDRs). The overall binding activity of the antigen binding fragment is often dictated by the sequence of the CDRs. The FRs often play a role in the proper positioning and alignment in three dimensions of the CDRs for optimal antigen binding.

Antibodies and/or antigen binding fragments of the present invention may originate, for example, from a mouse, a rat or any other mammal or from other sources such as through recombinant DNA technologies.

Further scope, applicability and advantages of the present invention will become apparent from the non-restrictive detailed description given hereinafter. It

should be understood, however, that this detailed description, while indicating exemplary embodiments of the invention, is given by way of example only, with reference to the accompanying drawings.

DETAILED DESCRIPTION OF THE INVENTION

The expression profile of Siglec-15 in osteoclasts and normal tissues

The present invention relates to the use of monoclonal antibodies to target osteoclasts found in various bone related disease where severe bone loss is observed due to increased activity of the osteoclasts. In order to direct the antibodies to the osteoclasts, the identification of osteoclast-specific antigens that are expressed at the cell surface of the cells must be carried out. There are several technologies that are available to identify cell-specific antigens and the method that was used to identify Siglec-15 in differentiating osteoclasts that were treated with RANKL, an innovative discovery platform called Subtractive Transcription-based Amplification of mRNA (STAR), is described in the published patent application No. PCT/CA2007/000210.

Analysis of the human osteoclast STAR libraries yielded many genes that encode secreted and cell surface proteins. One of these, termed AB-0326, contained an open reading frame that encoded a polypeptide of 328 amino acids, corresponding to SEQ ID NO:2 that was encoded by a cDNA of 987 base pairs with the nucleotide sequence shown in SEQ ID NO:1. A search of publicly available databases revealed that the AB-0326 nucleotide sequence was identical to that of a human gene called CD33 antigen-like 3 (CD33L3). CD33L3 was later found to be a member of the Siglec family of sialic acid binding proteins and was renamed Siglec-15 based on homology to other Siglecs (Crocker *et al.*, 2007). Based on this information, the mouse orthologue was isolated and sequenced and found to be approximately 85% identical to the human sequence at the amino acid level. SEQ ID NO:3 and SEQ ID NO:4 show the sequences of cDNA and polypeptide of the murine Siglec-15, respectively. Bioinformatic analysis predicted a type I membrane-anchored protein that presents its functional domain to the extracellular compartment. As with other Siglec sequences, an amino-terminal signal peptide (located between amino acids 1 and 19 of SEQ ID NO:2) targets the protein to the membrane of cells and the final processed protein is anchored to the membrane via a single trans-membrane helix located at the carboxy-terminus (located between

amino acids 261 and 283 of SEQ ID NO:2). The V-set Ig domain is located between amino acids 49 and 165 of SEQ ID NO:2 whereas the C2-set Ig domain is located between amino acids 178 and 244 of SEQ ID NO:2.

The present invention relates to the function of Siglec-15 during the differentiation of osteoclasts. Previous findings (Sooknanan et al. 2007) established that the transcript encoding human Siglec-15 was significantly upregulated in response to RANKL. This determination was performed on RNA macroarrays that contained spotted total RNA samples from several different human osteoclast differentiation experiments from different human PBMNC donors. Furthermore, these studies (Sooknanan et al. 2007) revealed that the Siglec-15 transcript was expressed in only one normal tissue among a vast panel of 30 human normal tissues indicating a very high osteoclast specificity of the *Siglec-15* gene expression. Using more sensitive methods such as semi-quantitative RT-PCR, the expression of the Siglec-15 mRNA was stimulated within one day of RANKL treatment in many osteoclast samples indicating that the gene was expressed early in osteoclast precursor cells, prior to the commencement of cell fusion. Finally, the tissue expression profile of Siglec-15 was assessed by semi-quantitative RT-PCR and found to only be expressed in a single normal human tissue thus validating the macroarray results of Sooknanan et al. Taken together, these expression results underscore the strength of the Applicant's discovery approach in its ability to identify targets, as exemplified by Siglec-15, that are highly restricted to differentiating osteoclasts.

Based on the expression of Siglec-15 in the early stages of differentiation of osteoclasts, its limited expression in normal tissues, and a critical biological role for Siglec-15 in the activity of osteoclasts, Siglec-15 was chosen as a therapeutic target for the development of monoclonal antibodies for the detection, prevention, and treatment of bone-related diseases such as cancer-induced bone loss and osteoporosis.

Therefore, a variety of anti-Siglec-15 antibodies and immunologically functional fragments thereof, such as chimeric and humanized monoclonal antibodies, antibody fragments, single chain antibodies, domain antibodies, and polypeptides with an antigen-binding region, for targeting Siglec-15 are provided.

SEQ ID NO:2 *as antigen and epitopes derived from* SEQ ID NO:2

In international application No. PCT/CA2007/000210, the Applicant has come to the unexpected discovery that SEQ ID NO:2 is involved in osteoclast differentiation. This antigen may thus be useful for targeting cells expressing the antigen *in vitro* or *in vivo* and in the development of detection assays for measuring the antigen *in vitro* or *in vivo*.

The present invention therefore provides an antigen useful for generating specific antibodies and/or specific for cells expressing SEQ ID NO:2. The antigen or epitope may comprise a fragment of at least 10 amino acids (and up to the total length) of SEQ ID NO:2 or of a SEQ ID NO: 2 variant.

An exemplary antigen is the whole SEQ ID NO:2 protein or a variant form having at least 80% sequence identity with SEQ ID NO:2 or a fragment comprising at least 10 amino acids of SEQ ID NO:2 or of a SEQ ID NO:2 variant.

The antigen or the epitope described herein may be fused with a carrier such as keyhole limpet (KHL), bovine serum albumin (BSA), ovalbumin (OVA) or else in order to generate antibodies and antigen binding fragments.

The present invention also provides an epitope comprised within amino acid 20 to 259 of SEQ ID NO:2 to generate antibodies and antigen binding fragments described herein. The epitope may comprise a fragment of at least 10 amino acids comprised within amino acids 20 to 259 of SEQ ID NO:2 or a corresponding portion of a SEQ ID NO.:2 variant.

The present invention further provides a composition for generating antibodies to SEQ ID NO:2 or to a SEQ ID NO:2 variant, the composition may comprise an epitope of SEQ ID NO:2 comprised within amino acids 20 to 259 of SEQ ID NO:2 or a corresponding portion of a SEQ ID NO:2 variant and a carrier.

Exemplary embodiments of compositions are pharmaceutical composition for generating antibodies against SEQ ID NO:2 or against a SEQ ID NO:2 variant. The pharmaceutical composition may comprise an epitope of SEQ ID NO:2 comprised within amino acids 20 to 259 of SEQ ID NO:2 or a corresponding portion of a SEQ ID NO:2 variant and a pharmaceutically acceptable carrier.

In yet a further aspect the invention provides a method for generating antibodies against SEQ ID NO:2 or against a SEQ ID NO:2 variant. The method may comprise administering a polypeptide comprising an epitope of SEQ ID NO:2 comprised within amino acids 20 to 259 of SEQ ID NO:2 or a corresponding portion of a SEQ ID NO:2 variant.

In an additional aspect, the present invention provides the use of an epitope of SEQ ID NO:2 comprised within amino acids 20 to 259 of SEQ ID NO:2 or a corresponding portion of a SEQ ID NO:2 variant for generating antibodies against SEQ ID NO:2 or against a SEQ ID NO:2 variant.

Exemplary embodiments of SEQ ID NO.:2 variant having 80% identity with SEQ ID NO.:2 include for example and without limitation, SEQ ID NO.:4 as well as other analogues that are published in databases under gene bank accession numbers or NCBI reference sequence: AAY40743.1, XP_512109.2, XP_001089000.1, XP_601064.4, NP_001094508.1, XP_855238.1, XP_574176.2 and EAX01462.1.

Antibodies and antigen binding fragments that binds to SEQ ID NO:2 or to SEQ ID NO:2 variant

Antibodies were initially isolated from Fab libraries for their specificity towards the antigen of interest. Comparison of the amino acid sequences of the light chain variable domains or the heavy chain variable domains of antibodies showing the greatest characteristics allowed us to derive consensus sequences within the CDRs and within the variable regions. The consensus for CDRs are provided in SEQ ID Nos:148-158 and 197-210. The consensus for the variable regions are provided in SEQ ID Nos.:191-196.

The variable regions described herein may be fused with constant regions of a desired species thereby allowing recognition of the antibody by effector cells of the desired species. The constant region may originate, for example, from an IgG1, IgG2, IgG3, or IgG4 subtype. Cloning or synthesizing a constant region in frame with a variable region is well within the scope of a person of skill in the art and may be performed, for example, by recombinant DNA technology.

In certain embodiments of the present invention, antibodies that bind to SEQ ID NO:2 may be of the IgG1, IgG2, IgG3, or IgG4 subtype. More specific embodiments of the invention relates to an antibody of the IgG1 subtype. The antibody may be a humanized antibody of the IgG1 subtype that is biologically active in mediating antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cytotoxicity (CMC), or associated with immune complexes. The typical ADCC involves activation of natural killer (NK) cells and is reliant on the recognition of antibody-coated cells by Fc receptors on the surface of the NK cells. The Fc

receptors recognize the Fc domain of antibodies such as is present on IgG1, which bind to the surface of a target cell, in particular a bone cell that expresses an antigen, such as SEQ ID NO:2. Once bound to the Fc receptor of IgG the NK cell releases cytokines and cytotoxic granules that enter the target cell and promote cell death by triggering apoptosis.

The present invention described a collection of antibodies that bind to SEQ ID NO:2. In certain embodiments, the antibodies may be selected from the group consisting of polyclonal antibodies, monoclonal antibodies such as chimeric or humanized antibodies, antibody fragments such as antigen binding fragments, single chain antibodies, domain antibodies, and polypeptides with an antigen binding region.

The present invention therefore provides in another aspect thereof, an isolated antibody or antigen binding fragment comprising a light chain variable domain having;

a. a CDRL1 sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:75, SEQ ID NO:81, SEQ ID NO:87, SEQ ID NO:93, SEQ ID NO:99, SEQ ID NO:105, SEQ ID NO:111, SEQ ID NO:173, SEQ ID NO:179 and SEQ ID NO:185 ;
b. a CDRL2 sequence selected from the group consisting of SEQ ID NO:70, SEQ ID NO:76. SEQ ID NO:82, SEQ ID NO:88, SEQ ID NO:94, SEQ ID NO:100, SEQ ID NO:106, SEQ ID NO:112, SEQ ID NO:174, SEQ ID NO:180 and SEQ ID NO:186 and/or;
c. a CDRL3 sequence selected from the group consisting of SEQ ID NO:71, SEQ ID NO:77, SEQ ID NO:83, SEQ ID NO:89, SEQ ID NO:95, SEQ ID NO:101, SEQ ID NO:107, SEQ ID NO:113, SEQ ID NO:175, SEQ ID NO:181 and SEQ ID NO:187.

The isolated antibody or antigen binding fragment may also comprise a heavy chain variable domain having;

a. a CDRH1 sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:78, SEQ ID NO:84, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:102, SEQ ID NO:108, SEQ ID NO:114, SEQ ID NO:176, SEQ ID NO:182 and SEQ ID NO:188;
b. a CDRH2 sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:79, SEQ ID NO:85, SEQ ID NO:91, SEQ ID

NO:97, SEQ ID NO:103, SEQ ID NO:109, SEQ ID NO:115, , SEQ ID NO:177, SEQ ID NO:183 and SEQ ID NO:189 and/or;

c. a CDRH3 sequence selected from the group consisting of SEQ ID NO:74, SEQ ID NO:80, SEQ ID NO:86, SEQ ID NO:92, SEQ ID NO:98, SEQ ID NO:104, SEQ ID NO:110, SEQ ID NO:116 , SEQ ID NO:178, SEQ ID NO:184 and SEQ ID NO:190.

In a further aspect, the present invention provides an isolated antibody or antigen binding fragment which may comprise a light chain variable domain having;

a) a CDRL1 which may have at least 80% identity with a CDRL1 sequence selected from the group consisting of SEQ ID NO.:148, SEQ ID NO.:69, SEQ ID NO.:75 and SEQ ID NO.:105

b) a CDRL2 which may have at least 80% identity with a CDRL2 sequence selected from the group consisting of SEQ ID NO.:149, SEQ ID NO.:150, SEQ ID NO.:76, SEQ ID NO.:82 and SEQ ID NO.:106, or;

c) a CDRL3 which may have at least 80% identity with a CDRL3 sequence selected from the group consisting of SEQ ID NO.:151, SEQ ID NO.:152, SEQ ID NO.:77, SEQ ID NO.:83, SEQ ID NO.:95, SEQ ID NO.:107 and SEQ ID NO.:152.

In yet a further aspect, the present invention provides an isolated antibody or antigen binding fragment, wherein the antibody comprises a heavy chain variable domain having;

a) a CDRH1 which may have at least 80% identity with a CDRH1 sequence selected from the group consisting of SEQ ID NO.:153, SEQ ID NO.:154, SEQ ID NO.:84, SEQ ID NO.:96 and SEQ ID NO.:102;

b) a CDRH2 which may have at least 80% identity with a CDRH2 sequence selected from the group consisting of SEQ ID NO.:155, SEQ ID NO.:156, SEQ ID NO.:157, SEQ ID NO.:73, SEQ ID NO.:79, SEQ ID NO.:85, SEQ ID NO.:97, SEQ ID NO.:103 and SEQ ID NO.:109, or;

c) a CDRH3 which may have at least 80% identity with a CDRH3 sequence selected from the group consisting of SEQ ID NO.:158,

SEQ ID NO.:74, SEQ ID NO.:98, SEQ ID NO.:104, SEQ ID NO.:110 and SEQ ID NO.:116.

In an exemplary embodiment, the antibody or antigen binding fragment may comprise any individual CDR or a combination of CDR1, CDR2 and/or CDR3 of the light chain variable region. The CDR3 may more particularly be selected. Combination may include for example, CDRL1 and CDRL3; CDRL1 and CDRL2; CDRL2 and CDRL3 and; CDRL1, CDRL2 and CDRL3.

In another exemplary embodiment, the antibody or antigen binding fragment may comprise any individual CDR or a combination of CDR1, CDR2 and/or CDR3 of the heavy chain variable region. The CDR3 may more particularly be selected. Combination may include for example, CDRH1 and CDRH3; CDRH1 and CDRH2; CDRH2 and CDRH3 and; CDRH1, CDRH2 and CDRH3.

In accordance with the present invention, the antibody or antigen binding fragment may comprise at least two CDRs of a CDRL1, a CDRL2 or a CDRL3.

Also in accordance with the present invention, the antibody or antigen binding fragment may comprise one CDRL1, one CDRL2 and one CDRL3.

Further in accordance with the present invention, the antibody or antigen binding fragment may comprise:

a. At least two CDRs of a CDRL1, CDRL2 or CDRL3 and;
b. At least two CDRs of a CDRH1, one CDRH2 or one CDRH3.

The antibody or antigen binding fragment may more preferably comprise one CDRL1, one CDRL2 and one CDRL3.

The antibody or antigen binding fragment may also more preferably comprise one CDRH1, one CDRH2 and one CDRH3.

In another aspect the present invention provides an isolated antibody or antigen binding fragment comprising a heavy chain variable domain having;

a. a CDRH1 sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:78, SEQ ID NO:84, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:102, SEQ ID NO:108, SEQ ID NO:114, SEQ ID NO:176, SEQ ID NO:182 and SEQ ID NO:188;
b. a CDRH2 sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:79, SEQ ID NO:85, SEQ ID NO:91, SEQ ID NO:97, SEQ ID NO:103, SEQ ID NO:109, SEQ ID NO:115, SEQ ID NO:177, SEQ ID NO:183 and SEQ ID NO:189 and/or;

c. a CDRH3 sequence selected from the group consisting of SEQ ID NO:74, SEQ ID NO:80, SEQ ID NO:86, SEQ ID NO:92, SEQ ID NO:98, SEQ ID NO:104, SEQ ID NO:110, SEQ ID NO:116, SEQ ID NO:178, SEQ ID NO:184 and SEQ ID NO:190.

In accordance with the present invention, the antibody or antigen binding fragment may comprise one CDRH1, one CDRH2 or one CDRH3.

In accordance with the present invention, the antibody or antigen binding fragment may also comprise one CDRH1, one CDRH2 and one CDRH3.

When only one of the light chain variable domain or the heavy chain variable domain is available, an antibody or antigen-binding fragment may be reconstituted by screening a library of complementary variable domains using methods known in the art (Portolano et al. The Journal of Immunology (1993) 150:880-887, Clarkson et al., Nature (1991) 352:624-628).

Also encompassed by the present invention are polypeptides or antibodies comprising variable chains having at least one conservative amino acid substitution in at least one of the CDRs described herein.

Also encompassed by the present invention are polypeptides or antibodies comprising variable chains having at least one conservative amino acid substitution in at least two of the CDRs.

Also encompassed by the present invention are polypeptides or antibodies comprising variable chains having at least one conservative amino acid substitution in the 3 CDRs.

Also encompassed by the present invention are polypeptides or antibodies comprising variable chains having at least two conservative amino acid substitution in at least one of the CDRs.

Also encompassed by the present invention are polypeptides or antibodies comprising variable chains having at least two conservative amino acid substitution in at least two of the CDRs.

Also encompassed by the present invention are polypeptides or antibodies comprising variable chains having at least two conservative amino acid substitution in the 3 CDRs.

In another aspect, the present invention relates to a polypeptide, antibody or antigen binding fragment comprising (on a single polypeptide chain or on separate polypeptide chains) at least one complementarity-determining region of a light chain

variable domain and at least one complementarity-determining region of a heavy chain variable domain of one of the antibodies or antigen binding fragment described herein.

The present invention relates in another aspect thereof to antibodies that may comprise (on a single polypeptide chain or on separate polypeptide chains) all six complementarity-determining region (CDR) of the antibody or antigen binding fragment described herein.

The antibodies or antigen binding fragment of the present invention may further comprise additional amino acids flanking the amino and/or carboxy region of the CDR(s). Those additional amino acids may be identical to the framework regions of the corresponding antibodies described herein or may include, for example, conservative amino acid substitution.

In accordance with an embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRL1 sequence comprising or consisting of formula:

$RSX_{1a}X_{2a}SLLHSNGX_{3a}TYLY$ (SEQ ID NO.:148),

Wherein X_{1a} may be, for example, a neutral hydrophilic amino acid;

Wherein X_{2a} may be, for example, lysine or glutamic acid

wherein X_{3a} may be, for example, an hydrophobic amino acid or asparagine.

In a more specific embodiment, X_{1a} may be, for example, serine.

In a more specific embodiment, X_{2a} may be, for example, lysine.

More particularly X_{3a} may be, for example, isoleucine or valine.

In a more specific embodiment, X_{3a} may be isoleucine.

In accordance with yet another embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRL1 sequence comprising or consisting of formula:

$RASX_{a10}NIX_{b10}X_{c10}YLA$ (SEQ ID NO.:197)

Wherein X_{a10} may be any amino acid or for example G or E;

X_{b10} may be any amino acid or for example Y or H, and;

X_{c10} may be any amino acid or for example S or N.

In accordance with yet another embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRL1 sequence comprising or consisting of formula: CDRL1 of formula $RSSX_{1x}SLLHSNGX_{2x}TYLY$ (SEQ ID NO.:201) wherein X_{1x} and X_{2x} are as defined herein.

In accordance with yet another embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRL1 sequence comprising or consisting of formula: CDRL1 of formula $RSX_{a6}KSLLHSNGNTYLY$ (SEQ ID NO.:202) wherein X_{a6} is as defined herein.

The antibody or antigen binding fragment may also comprise, for example, a CDRL1 sequence selected from those comprising or consisting of SEQ ID NO.:75, SEQ ID NO.:69, SEQ ID NO.:105 and other CDRL1 listed in Table 3 or Table 5B.

In accordance with another embodiment, the antibody or antigen binding fragment may comprise a CDRL2 sequence comprising or consisting of formula:

$X_{1b}MSNLAS$ (SEQ ID NO.:149),

wherein X_{1b} may be, for example, a basic amino acid.

More particularly, X_{1b} may be, for example, glutamine or asparagine.

In a more specific embodiment, X_{1b} may be glutamine.

In accordance with yet another embodiment, the antibody or antigen binding fragment may comprise a CDRL2 sequence comprising or consisting of formula:

$RX_{1c}SNLX_{2c}S$ (SEQ ID NO.:150),

wherein X_{1c} may be, for example, methionine or threonine and wherein X_{2c} may be, for example, an hydrophobic amino acid.

More particularly, X_{2c} may be, for example, alanine or valine.

In a more specific embodiment, X_{1c} may be, for example, methionine.

In a more specific embodiment, X_{2c} may be, for example, alanine.

In accordance with yet another embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRL2 sequence comprising or consisting of formula:

$NAKTLX_{a11}X_{b11}$ (SEQ ID NO.:198)

X_{a11} may be any amino acid or for example P or A, and;

X_{b11} may be any amino acid or for example an acidic amino acid such as E or D.

The antibody or antigen binding fragment may also comprise, for example, a CDRL2 sequence selected from those comprising or consisting of SEQ ID NO.:76, SEQ ID NO.:82, SEQ ID NO.:106 and other CDRL2 listed in Table 3 or Table 5B..

In accordance with yet another embodiment, the antibody or antigen binding fragment may comprise a CDRL3 sequence comprising or consisting of formula:

$X_{1d}QX_{2d}LEX_{3d}PX_{4d}T$ (SEQ ID NO.:151)

wherein X_{1d} may be, for example, an hydrophobic amino acid;

wherein X_{2d} may be, for example, a basic amino acid;

wherein X_{3d} may be, for example, tyrosine or leucine, and;

wherein X_{4d} may be, for example, an aromatic amino acid.

More particularly, X_{1d} may be, for example, methionine or alanine, In a more specific embodiment, X_{1d} may be, for example, methionine.

More particularly, X_{2d} may be, for example histidine or asparagine. In a more specific embodiment, X_{2d} may be, for example, histidine.

In a more specific embodiment, X_{3d} may be, for example, tyrosine.

More particularly, X_{4d} may be, for example, tyrosine or phenylalanine. In a more specific embodiment, X_{4d} may be, for example, tyrosine.

In accordance with an additional embodiment, the antibody or antigen binding fragment may comprise a CDRL3 sequence comprising or consisting of formula:

$QQWSSNPX_{1e}T$ (SEQ ID NO.:152)

Wherein X_{1e} is proline or leucine.

In accordance with yet another embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRL3 sequence comprising or consisting of formula:

$QHYGX_{a12}PLT$ (SEQ ID NO.:199)

X_{a12} may be any amino acid or a hydrophobic amino acid such as for example A or V.

In accordance with a further embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRL3 sequence comprising or consisting of formula: $X_{a8}QX_{b8}LEX_{c8}PYT$ (SEQ ID NO.:203) wherein X_{a8}, X_{b8} and X_{c8} are as defined herein.

In accordance with yet a further embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRL3 sequence comprising or consisting of formula: $QHHYGX_{a4}PLT$ (SEQ ID NO.:204) wherein X_{a4} is as defined herein.

The antibody or antigen binding fragment may also comprise, for example, a CDRL3 sequence selected from those comprising or consisting of SEQ ID NO.:77, SEQ ID NO.:83, SEQ ID NO.:95, SEQ ID NO.:107, SEQ ID NO.:152 and other CDRL3 listed in Table 3 or Table 5B.

In accordance with an additional embodiment, the antibody or antigen binding fragment may comprise a CDRH1 sequence comprising or consisting of formula:

$GYTFX_{1f}X_{2f}YX_{3f}MX_{4f}$ (SEQ ID NO.:153)

wherein X_{1f} may be, for example, threonine or asparagine;

wherein X_{2f} may be, for example, threonine, arginine, serine or aspartic acid;

wherein X_{3f} may be, for example, tryptophan or asparagine, aspartic acid or glutamic acid, and;

wherein X_{4f} may be, for example, tyrosine, histidine or aspartic acid.

In a more specific embodiment, X_{1f} may be, for example, threonine.

In a more specific embodiment, X_{2f} may be, for example, serine.

In a more specific embodiment, X_{3f} may be, for example, tryptophan.

In a more specific embodiment, X_{4f} may be, for example, histidine.

In accordance with yet an additional embodiment, the antibody or antigen binding fragment may comprise a CDRH1 sequence comprising or consisting of formula:

$GYTFTDYX_{5f}MH$ (SEQ ID NO.:154)

Wherein X_{5f} may be, for example, an acidic amino acid.

More particularly, X_{5f} may be, for example, glutamic acid or aspartic acid. In a more specific embodiment, X_{5f} may be, for example, aspartic acid.

In accordance with a further embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRH1 sequence comprising or consisting of formula: $GYTFTX_{1l}YWMH$ (SEQ ID NO.:205) wherein X_{1l} is as defined herein.

In accordance with yet a further embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRH1 sequence comprising or consisting of formula: $GYTFTDYX_{1s}MH$ (SEQ ID NO.:208) wherein X_{1s} is as defined herein.

The antibody or antigen binding fragment may also comprise, for example, a CDRH1 sequence selected from those comprising or consisting of SEQ ID NO.:84, SEQ ID NO.:96, SEQ ID NO.:102 and other CDRH1 listed in Table 3 or Table 5A.

In accordance with a further embodiment, the antibody or antigen binding fragment may comprise a CDRH2 sequence comprising or consisting of formula:

$LINPX_{1g}NX_{2g}RX_{3g}N$ (SEQ ID NO.:155)

Wherein X_{1g} may be, for example, a neutral hydrophilic amino acid;

Wherein X_{2g} may be, for example, alanine or glycine, and;

Wherein X_{3g} may be, for example, proline or threonine.

More particularly, X_{1g} may be, for example, serine or threonine. In a more specific embodiment, X_{1g} may be, for example, threonine.

In a more specific embodiment, X_{2g} may be, for example, glycine.

In a more specific embodiment, X_{3g} may be, for example, threonine.

In accordance with yet a further embodiment, the antibody or antigen binding fragment may comprise a CDRH2 sequence comprising or consisting of formula:

X_{1h}IDPETGGTA (SEQ ID NO.:156)

Wherein X_{1h} may be, for example, alanine or threonine.

In accordance with a more specific embodiment, X_{1h} may be, for example, threonine.

In accordance with yet a further embodiment, the antibody or antigen binding fragment may comprise a CDRH2 sequence comprising or consisting of formula:

$EIX_{1i}PX_{2i}X_{3i}SX_{4i}X_{5i}N$ (SEQ ID NO.:157)

Wherein X_{1i} may be, for example, aspartic acid or asparagine;

Wherein X_{2i} may be, for example, aspartic acid or serine;

Wherein X_{3i} may be, for example,aspartic acid or serine;

Wherein X_{4i} may be, for example,tyrosine or threonine, and;

Wherein X_{5i} may be, for example,threonine or isoleucine.

In accordance with yet another embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRH2 sequence comprising or consisting of formula:

AX_{a13}YPGNGDSR (SEQ ID NO.:200)

X_{a13} may be any amino acid or a hydrophobic amino acid such as I or V.

In accordance with an additional embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRH2 sequence comprising or consisting of formula: X_{1t}IDPETGGTA (SEQ ID NO.:206) wherein X_{1t} is as defined herein.

In accordance with yet an additional embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRH2 sequence comprising or consisting of formula:$LINPX_{1m}NX_{2m}RX_{3m}N$ (SEQ ID NO.:207) wherein X_{1m}, X_{2m} and X_{3m} are as defined herein.

In accordance with a further embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRH2 sequence comprising or consisting of formula: X_{1t}IDPETGGTA (SEQ ID NO.:209) wherein X_{1t} is as defined herein.

The antibody or antigen binding fragment may also comprise, for example, a CDRH2 sequence selected from those comprising or consisting of SEQ ID NO.:73, SEQ ID NO.:79, SEQ ID NO.:85, SEQ ID NO.:97, SEQ ID NO.:103 and SEQ ID NO.:109 and other CDRH2 listed in Table 3 or Table 5A.

In accordance with an additional embodiment, the antibody or antigen binding fragment may comprise a CDRH3 sequence comprising or consisting of formula:

$TX_{1j}FYYX_{2j}X_{3j}X_{4j}$NYDVGFAY (SEQ ID NO.:158)

Wherein X_{1j} may be, for example, a neutral hydrophilic amino acid;

Wherein X_{2j} may be, for example, a neutral hydrophilic amino acid;

Wherein X_{3j} may be, for example, tyrosine or histidine, and;

Wherein X_{4j} may be, for example, tyrosine or serine.

More particularly, X_{1j} may be, for example, serine or threonine. In a more specific embodiment, X_{1j} may be, for example, serine.

More particularly, X_{2j} may be, for example, serine or threonine. In a more specific embodiment, X_{2j} may be, for example, threonine.

In a more specific embodiment, X_{3j} may be, for example, tyrosine.In a more specific embodiment, X_{4j} may be, for example, serine.

In accordance with a further embodiment of the present invention, the antibody or antigen binding fragment may comprise a CDRH3 sequence comprising or consisting of formula: $TX_{1v}FYYX_{2v}X_{3v}X_{4v}$NYDVGFAY (SEQ ID NO.:210) wherein X_{1v}, X_{2v}, X_{3v} and X_{4v} are as defined herein.

The antibody or antigen binding fragment may comprise, for example, a CDRH3 sequence selected from those comprising or consisting of SEQ ID NO.:74, SEQ ID NO.:98, SEQ ID NO.:104, SEQ ID NO.:110, SEQ ID NO.:116 and other CDRH3 listed in Table 3 or Table 5A.

The framework region of the heavy and/or light chains described herein may be derived from one or more of the framework regions illustrated herein. The antibody or antigen binding fragments may thus comprise one or more of the CDRs described herein (e.g., selected from the specific CDRs or from consensus CDRs

SEQ ID NOs.: 148-158 and 197-210) and framework regions originating from the light or heavy chain variable regions illustrated herein.

In an embodiment of the invention, the antibody or antigen binding fragment of the present invention may comprise a heavy chain variable region (or a fragment) having formula :

$X_{1k}X_{2k}QX_{3k}QQX_{4k}X_{5k}X_{6k}EX_{7k}VX_{8k}$PGASVKLSCKAS**GYTFTX$_{1l}$YWMH**WVKQRPGQGLEWIG**LINPX$_{1m}$NX$_{2m}$RX$_{3m}$N**YNEX$_{1n}$FX$_{2n}$X$_{3n}$KATLTVDKSSSTAYMX$_{4n}$LSSLTSEDSAVYYC**ARGGDGDYFDY**WGQGTTLTVSS (SEQ ID NO.:191)

Wherein X_{1k} may be for example Q or E;

X_{2k} may be any amino acid or a hydrophobic amino acid such as for example V or I;

X_{3k} may be any amino acid or a hydrophobic amino acid such as for example V or L;

X_{4k} may be any amino acid or for example P or S;

X_{5k} may be any amino acid or for example R or G;

X_{6k} may be any amino acid or for example A or T;

X_{7k} may be any amino acid or a hydrophobic amino acid such as for example L or I;

X_{8k} may be any amino acid or a basic amino acid such as for example R or K;

X_{1l} may be any amino acid or a neutral hydrophilic amino acid such as for example for example S or T;

X_{1m} may be any amino acid or a neutral hydrophilic amino acid such as for example T or S;

X_{2m} may be any amino acid or for example G or A;

X_{3m} may be any amino acid or for example P or T;

X_{1n} may be any amino acid or a basic amino acid such as for example K or R;

X_{2n} may be any amino acid or a basic amino acid such as for example N or K;

X_{3n} may be any amino acid or for example N or a neutral hydrophilic amino acid such as S or T and;

X_{4n} may be any amino acid or a basic amino acid such as for example Q or H.

In another embodiment of the invention, the antibody or antigen binding fragment of the present invention may comprise a heavy chain variable region (or a fragment) having formula :

$X_{10}VX_{2o}$LQQSGAELARPGASVKFSCKAS**GYTFTRNWIQ**WVKQRPGQGLEWIG**AX$_{a13}$YPGNGDSR**YTQKFKGKATLTADKSSX$_{1q}$TAYMQLX$_{2q}$X$_{3q}$LX$_{4q}$SEDSAVYYC**ARLAGNYAYYFDY**WGQGTALTVSS (SEQ ID NO.:192)

Wherein X_{1o} may be for example Q or D;

X_{2o} may be any amino acid or a basic amino acid such as for example K or Q;

X_{a13} may be any amino acid or a hydrophobic amino acid such as for example I or V;

X_{1q} may be any amino acid or for example S or N;

X_{2q} may be any amino acid or for example S or N;

X_{3q} may be any amino acid or for example G or S and;

X_{4q} may be any amino acid or for example A or S.

In yet another embodiment of the invention, the antibody or antigen binding fragment of the present invention may comprise a heavy chain variable region (or a fragment) having formula :

$X_{1r}X_{2r}X_{3r}$LQQSGX_{4r}ELVRPGASVTLSCKAS**GYTFTDYX$_{1s}$MH**WVKQTPVHGLEWIG**X$_{1t}$IDPETGGTA**YNQKFKGKATLTADX$_{1u}$SSX$_{2u}$TAYMELSSLTSEDSAVYYC**TX$_{1v}$FYYX$_{2v}$X$_{3v}$X$_{4v}$NYDVGFAY**WGQGTLVTVSA (SEQ ID NO.:193)

Wherein X_{1r} may be for example E or Q;

X_{2r} may be any amino acid or a hydrophobic amino acid such as for example A or I;

X_{3r} may be any amino acid or for example Y or Q;

X_{4r} may be any amino acid or a hydrophobic amino acid such as for example A or V;

X_{1s} may be any amino acid or an acidic amino acid such as for example D or E;

X_{1t} may be any amino acid or for example A or T;

X_{1u} may be any amino acid or a basic amino acid such as for example K or R;

X_{2u} may be any amino acid or a neutral hydrophilic amino acid such as for example S or T;

X_{1v} may be any amino acid or a neutral hydrophilic amino acid such as for example S or T;

X_{2v} may be any amino acid or a neutral hydrophilic amino acid such as for example T or S;

X_{3v} may be any amino acid or for example Y or H and;

X_{4v} may be any amino acid or for example S or Y.

In an additional embodiment, the antibody or antigen binding fragment of the present invention may comprise a light chain variable region (or a fragment) having formula :

DIVMTX$_{1w}$AX$_{2w}$FSNPVX$_{3w}$LGTX$_{4w}$ASISC**RSSX$_{1x}$SLLHSNGX$_{2x}$TYLY**WYLQKPGQSP QLLIY**QMSNLAS**GVPDRFSX$_{1y}$SGSGTX$_{2y}$FTLRISRVEAEDVGVYYC**X$_{a8}$QX$_{b8}$LEX$_{c8}$P YT**FGX$_{a9}$GTKLEIK (SEQ ID NO.:194)

Wherein X_{1w} may be any amino acid or a basic amino acid such as for example Q or H;

X_{2w} may be any amino acid or a hydrophobic amino acid such as for example V or A;

X_{3w} may be any amino acid or for example T or I;

X_{4w} may be any amino acid or for example S or P;

X_{1x} may be any amino acid or for example E or K;

X_{2x} may be any amino acid or a hydrophobic amino acid such as for example V or I;

X_{1y} may be any amino acid or for example S or G;

X_{2y} may be any amino acid or for example D or A;

X_{a8} may be any amino acid or a hydrophobic amino acid such as for example M or A;

X_{b8} may be any amino acid or a basic amino acid such as for example N or H;

X_{c8} may be any amino acid or for example Y or L, and;

X_{a9} may be any amino acid or for example G or S.

In a further embodiment, the antibody or antigen binding fragment of the present invention may comprise a light chain variable region (or a fragment) having formula :

X_{1z}IQMTQSPASLSASVGETVTITC**RASX$_{a10}$NIX$_{b10}$X$_{c10}$YLA**WYQQKQGKSPQLLVY**N AKTLX$_{a11}$X$_{b11}$**GVX$_{a3}$X$_{b3}$RFSGSGSGTQX$_{c3}$SLKINX$_{d3}$LQPEDFGSYX$_{e3}$C**QHHYGX$_{a4}$PL T**FGX$_{a5}$GTKX$_{b5}$ELK (SEQ ID NO.:195)

Wherein X_{1z} may be any amino acid or for example D or N;

X_{a10} may be any amino acid or for example E or G;

X_{b10} may be any amino acid or for example Y or H;

X_{c10} may be any amino acid or for example S or N;

X_{a1111} may be any amino acid or for example P or A;

X_{b11} may be any amino acid or an acidic amino acid such as for example E or D;

X_{a3} may be any amino acid or for example P or S;

X_{b3} may be any amino acid or for example V or S;

X_{c3} may be any amino acid or an aromatic amino acid such as for example F or Y;

X_{d3} may be any amino acid or for example N or S;

X_{e3} may be any amino acid or for example H or Y;

X_{a4} may be any amino acid or a hydrophobic amino acid such as for example A or V;

X_{a5} may be any amino acid or for example S or A, and;

X_{b5} may be any amino acid or a hydrophobic amino acid such as for example V or L.

In yet a further embodiment, the antibody or antigen binding fragment of the present invention may comprise a light chain variable region (or a fragment) having formula : DIVMTQAAPSVPVTPGESVSISC**RSX$_{a6}$KSLLHSNGNTYLY**WFLQRPGQSPQLLIY**R MSNLAS**GVPDRFSGSGSGTAFTLRX$_{a7}$SRVEAEDVGVYYC**MQHLEYPFT**FGGGTK LEIK (SEQ ID NO.:196)

Wherein X_{a6} may be any amino acid or a neutral hydrophilic amino acid such as for example S or T, and;

X_{a7} may be any amino acid or a hydrophobic amino acid such as for example I or L.

Antibodies that bind to Siglec-15

In certain embodiments of the present invention, antibodies that bind to Siglec-15 are of the IgG1, IgG2, IgG3, or IgG4 subtype. In the preferred embodiment, the antibody is an antibody of the IgG2 subtype. In the present embodiment, the antibody is a humanized antibody of the IgG2 subtype that is biologically active in blocking the biological activity of normal Siglec-15 function on the surface of osteoclasts. Such blockage, for example, could prevent the association of Siglec-15 with its substrates, its ligands, itself, or other proteins on adjacent cells.

The present invention discloses a collection of antibodies that bind to Siglec-15. In certain embodiments, the antibodies consist of monoclonal antibodies and immunologically functional fragments thereof, such as chimeric and humanized monoclonal antibodies, antibody fragments, single chain antibodies, domain antibodies, and polypeptides with an antigen-binding region.

A typical antigen-binding site is comprised of the variable regions formed by the pairing of a light chain immunoglobulin and a heavy chain immunoglobulin. The structure of the antibody variable regions is very consistent and exhibits very similar structures. These variable regions are typically comprised of relatively homologous framework regions (FR) interspaced with three hypervariable regions termed Complementarity Determining Regions (CDRs). Although the overall binding activity of the antigen binding fragment is dictated by the sequence of the CDRs, the FRs play a critical role in the proper positioning and alignment in three dimensions of the CDRs for optimal antigen binding.

Table 1 discloses the sequences of the nucleotides and the amino acids corresponding to the complete light and heavy chain immunoglobulins of specific examples of anti-Siglec-15 antibodies.

TABLE 1 – Complete sequences of light and heavy chain immunoglobulins that bind to Siglec-15

Antibody designation	Chain type	Nucleotide sequence (SEQ ID NO:)	Amino acid sequence (SEQ ID NO:)
25A1	Light (L)	5	6
25A1	Heavy (H)	7	8
25B4	Light	9	10
25B4	Heavy	11	12
25B8	Light	13	14
25B8	Heavy	15	16
25C1	Light	17	18
25C1	Heavy	19	20
25D8	Light	21	22
25D8	Heavy	23	24
25E5	Light	25	26
25E5	Heavy	27	28
25E6	Light	29	30
25E6	Heavy	31	32
25E9	Light	33	34
25E9	Heavy	35	36

An antibody that can bind Siglec-15 may comprise any one L chain with any one H chain immunoglobulin that is listed in Table 1. In certain embodiments, the light chain of antibody 25A1 may be combined with the heavy chain of 25A1 or the heavy chain of 25B4 to form a complete antibody with Siglec-15-binding activity. In an exemplary embodiment of the present invention, the 25A1 L chain may be combined with the 25A1 H chain, the 25B4 L chain may be combined with the 25B4 H chain, the 25B8 L chain may be combined with the 25B8 H chain, the 25C1 L chain may be combined with the 25C1 H chain, the 2D8 L chain may be combined with the 25D8 H chain, the 25E5 L chain may be combined with the 25E5 H chain, the 25E6 L chain may be combined with the 25E6 H chain, or the 25E9 L chain may be combined with the 25E9 H chain. Additionally, some examples of antibodies or antigen binding fragment may consist of any combination of two L chains and any two H chains from the list of antibodies listed in Table 1.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 25A1 are shown in SEQ ID NOS:5 and 7, respectively, and the

corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 25A1 are shown in SEQ ID NOS:6 and 8, respectively. Thus, in an exemplary embodiment, an antibody that binds to Siglec-15 may comprise the light chain amino acid shown in SEQ ID NO:6 combined with the heavy chain amino acid sequence shown in SEQ ID NO:8. In another embodiment, the antibody may comprise two identical or substantially identical 25A1 light chains comprising SEQ ID NO:6 or a variant thereof and two identical or substantially identical 25A1 heavy chains comprising SEQ ID NO:8 or a variant thereof.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 25B4 are shown in SEQ ID NOS:9 and 11, respectively, and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 25B4 are shown in SEQ ID NOS:10 and 12, respectively. Thus, in an exemplary embodiment, an antibody that binds to Siglec-15 may comprise the light chain amino acid shown in SEQ ID NO:10 combined with the heavy chain amino acid sequence shown in SEQ ID NO:12. In another embodiment, the antibody may comprise two identical or substantially identical 25B4 light chains comprising SEQ ID NO:10 or a variant thereof and two identical or substantially identical 25B4 heavy chains comprising SEQ ID NO:12 or a variant thereof.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 25B8 are shown in SEQ ID NOS:13 and 15, respectively and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 25B8 are shown in SEQ ID NOS:14 and 16, respectively. Thus, in an exemplary embodiment, an antibody that binds to Siglec-15 may comprise the light chain amino acid shown in SEQ ID NO:14 combined with the heavy chain amino acid sequence shown in SEQ ID NO:16. In another embodiment, the antibody may comprise two identical or substantially identical 25B8 light chains comprising SEQ ID NO:14 or a variant thereof and two identical or substantially identical 25B8 heavy chains comprising SEQ ID NO:16 or a variant thereof.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 25C1 are shown in SEQ ID NOS:17 and 19, respectively, and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 25C1 are shown in SEQ ID NOS:18 and 20, respectively. Thus, in an exemplary embodiment, an antibody that binds to Siglec-15 may comprise the light chain amino acid shown in SEQ ID NO:18 combined with the heavy chain amino acid

sequence shown in SEQ ID NO:20. In another embodiment, the antibody may comprise two identical or substantially identical 25C1 light chains comprising SEQ ID NO:18 or a variant thereof and two identical or substantially identical 25C1 heavy chains comprising SEQ ID NO:20 or a variant thereof.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 25D8 are shown in SEQ ID NOS:21 and 23, respectively, and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 25D8 are shown in SEQ ID NOS:22 and 24, respectively. Thus, in an exemplary embodiment, an antibody that binds to Siglec-15 may comprise the light chain amino acid shown in SEQ ID NO:22 combined with the heavy chain amino acid sequence shown in SEQ ID NO:24. In another embodiment, the antibody may comprise two identical or substantially identical 25D8 light chains comprising of SEQ ID NO:22 or a variant thereof and two identical or substantially identical 25D8 heavy chains comprising SEQ ID NO:24 or a variant thereof.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 25E5 are shown in SEQ ID NOS:25 and 27, respectively, and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 25E5 are shown in SEQ ID NOS:26 and 28, respectively. Thus, in an exemplary embodiment, an antibody that binds to Siglec-15 may comprise the light chain amino acid shown in SEQ ID NO:26 combined with the heavy chain amino acid sequence shown in SEQ ID NO:28. In another embodiment, the antibody may comprise two identical or substantially identical 25E5 light chains comprising SEQ ID NO:26 or a variant thereof and two identical or substantially identical 25E5 heavy chains comprising SEQ ID NO:28 or a variant thereof.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 25E6 are shown in SEQ ID NOS:29 and 31, respectively and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 25E6 are shown in SEQ ID NOS:30 and 32, respectively. Thus, in an exemplary embodiment, an antibody that binds to Siglec-15 may comprise the light chain amino acid shown in SEQ ID NO:30 combined with the heavy chain amino acid sequence shown in SEQ ID NO:32. In another embodiment, the antibody may comprise two identical or substantially identical 25E6 light chains comprising SEQ ID NO:30 or a variant thereof and two identical or substantially identical 25E6 heavy chains comprising SEQ ID NO:32 or a variant thereof.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 25E9 are shown in SEQ ID NOS:33 and 35, respectively, and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 25E9 are shown in SEQ ID NOS:34 and 36, respectively. Thus, in an exemplary embodiment, an antibody that binds to Siglec-15 may comprise the light chain amino acid shown in SEQ ID NO:34 combined with the heavy chain amino acid sequence shown in SEQ ID NO:36. In another embodiment, the antibody may comprise two identical or substantially identical 25E9 light chains comprising SEQ ID NO:34 or a variant thereof and two identical or substantially identical 25E9 heavy chains comprising SEQ ID NO:36 or a variant thereof.

Variants of other anti-Siglec-15 antibodies or antigen binding fragments formed by the combination of light and/or heavy immunoglobulin chains may each independently have at least 80%, 85%, 90%, 95%, 97%, or 99% identity to the amino acid sequences listed in **Table 1** are also provided. In certain embodiments, the antibody variants may comprise at least one light chain and one heavy chain. In other instances, the antibody variants may comprise two identical or substantially identical light chains and two identical or substantially identical heavy chains. In accordance with the present invention, the region of variation may be located in the constant region or in the variable region. Also in accordance with the present invention, the region of variation may be located in the framework region.

Also encompassed by the present invention are antibodies comprising a light chain comprising one of the variable region of the light chain sequence listed in Table 1 or a variant thereof and a heavy chain comprising one of the variable region of the heavy chain sequence listed in Table 1 or a variant thereof. The light chain and heavy chain may comprise a constant domain. Combinations of light chains and heavy chains of Table **1** are also encompassed by the present invention.

Antibodies or antigen binding fragments that contain the light chain and heavy chain variable regions are also provided in the present invention. Additionally, certain embodiments include antigen binding fragments, variants, and derivatives of these light and heavy chain variable regions.

Yet other exemplary embodiments of the invention includes an isolated antibody or antigen binding fragment capable of specific binding to SEQ ID NO:2 or to a variant thereof, the antibody comprising:

a. the light chain variable domain defined in SEQ ID NO.:38 and the heavy chain variable domain defined in SEQ ID NO.:40;
b. the light chain variable domain defined in SEQ ID NO.:42 and the heavy chain variable domain defined in SEQ ID NO.:44;
c. the light chain variable domain defined in SEQ ID NO.:46 and the heavy chain variable domain defined in SEQ ID NO.:48;
d. the light chain variable domain defined in SEQ ID NO.:50 and the heavy chain variable domain defined in SEQ ID NO.:52;
e. the light chain variable domain defined in SEQ ID NO.:54 and the heavy chain variable domain defined in SEQ ID NO.:56,
f. the light chain variable domain defined in SEQ ID NO.:58 and the heavy chain variable domain defined in SEQ ID NO.:60;
g. the light chain variable domain defined in SEQ ID NO.:62 and the heavy chain variable domain defined in SEQ ID NO.:64;
h. the light chain variable domain defined in SEQ ID NO.:66 and the heavy chain variable domain defined in SEQ ID NO.:68;

It is to be understood herein, that the light chain variable region of the specific combination provided above may be changed for any other light chain variable region (especially those of Table 2). Similarly, the heavy chain variable region of the specific combination provided above may be changed for any other heavy chain variable region (especially those of Table 2).

Antibodies that contain the light chain and heavy chain variable regions are also provided in the present invention. Additionally, certain embodiments include antigen binding fragments, variants, and derivatives of these light and heavy chain variable regions. Examples of sequences present in these light and heavy chain variable regions are disclosed in Table 2.

Table 2 – Sequences of light and heavy chain variable regions that bind to Siglec-15

Antibody designation	Chain type	Nucleotide sequence (SEQ ID NO:)	Amino acid sequence (SEQ ID NO:)
25A1	Light (L)	37	38
25A1	Heavy (H)	39	40
25B4	Light	41	42
25B4	Heavy	43	44
25B8	Light	45	46
25B8	Heavy	47	48
25C1	Light	49	50

Antibody designation	Chain type	Nucleotide sequence (SEQ ID NO:)	Amino acid sequence (SEQ ID NO:)
25C1	Heavy	51	52
25D8	Light	53	54
25D8	Heavy	55	56
25E5	Light	57	58
25E5	Heavy	59	60
25E6	Light	61	62
25E6	Heavy	63	64
25E9	Light	65	66
25E9	Heavy	67	68
25B02	Light	161	162
25B02	Heavy	163	164
25D11	Light	165	166
25D11	Heavy	167	168
25E10	Light	169	170
25E10	Heavy	171	172

Therefore, antibodies and antigen binding fragments that bind to Siglec-15 may comprise one light chain variable region and one chain heavy variable region of the same designated antibody or in any combinations. For example, in an exemplary embodiment, an anti-Siglec-15 antibody or fragment may comprise the 25A1 light chain variable region (SEQ ID NO:38) and the 25A1 heavy chain variable region (SEQ ID NO:40). In an alternate embodiment, an anti-Siglec-15 antibody or fragment may comprise the 25A1 light chain variable region (SEQ ID NO:38) and the 25B4 heavy chain variable region (SEQ ID NO:44). In another embodiment, the anti-Siglec-15 antibodies may comprise two identical or substantially identical light chain variable regions and two identical or substantially identical heavy chain regions. In yet another embodiment, the anti-Siglec-15 antibodies may comprise two different light chain variable regions and two different heavy chain regions.

Variants of other anti-Siglec-15 antibodies formed by the combination of light and/or heavy chain variable regions that each have at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identity to the amino acid sequences listed in Table 2, Tables 5A and 5B are also provided. Those skilled in the art will also recognize that the anti-Siglec-15 antibody variants may include conservative amino acid changes, amino acid substitutions, deletions, or additions in the amino acid sequences of the light and/or heavy chain variable regions listed in Table 2.

Table 3 – Sequences of the light and heavy chain CDRs

Antibody designation	Chain type	CDR	SEQ ID NO:	Amino acid sequence
25A1	Light (L)	CDR1	69	SASSSVSYMY
25A1	Light	CDR2	70	RTSNLAS
25A1	Light	CDR3	71	QQWSSNPLT
25A1	Heavy (H)	CDR1	72	GYTFTRYWMD
25A1	Heavy	CDR2	73	EIDPSDSYTN
25A1	Heavy	CDR3	74	ARSGAYSSDYSYDGFAY
25B4	Light	CDR1	75	RSSKSLLHSNGITYLY
25B4	Light	CDR2	76	QMSNLAS
25B4	Light	CDR3	77	MQHLEYPYT
25B4	Heavy	CDR1	78	GYTFTSYWMH
25B4	Heavy	CDR2	79	LINPTNGRTN
25B4	Heavy	CDR3	80	ARGGDGDYFDY
25B8	Light	CDR1	81	RSTKSLLHSNGNTYLY
25B8	Light	CDR2	82	RMSNLAS
25B8	Light	CDR3	83	MQHLEYPFT
25B8	Heavy	CDR1	84	GYTFTDYDMH
25B8	Heavy	CDR2	85	TIDPETGGTA
25B8	Heavy	CDR3	86	TTFYYSHYNYDVGFAY
25C1	Light	CDR1	87	RSSKSLLHSNGNTYLY
25C1	Light	CDR2	88	RMSNLAS
25C1	Light	CDR3	89	MQHLEYPFT
25C1	Heavy	CDR1	90	GYTFTDYEMH
25C1	Heavy	CDR2	91	AIDPETGGTA
25C1	Heavy	CDR3	92	TSFYYTYYNYDVGFAY
25D8	Light	CDR1	93	RSSKSLLHSNGITYLY
25D8	Light	CDR2	94	QMSNLAS
25D8	Light	CDR3	95	AQNLELPYT
25D8	Heavy	CDR1	96	GYTFTSYWMH
25D8	Heavy	CDR2	97	LINPSNARTN
25D8	Heavy	CDR3	98	ARGGDGDYFDY
25E5	Light	CDR1	99	SASSSVSYMY
25E5	Light	CDR2	100	RTSNLVS
25E5	Light	CDR3	101	QQWSSNPPT
25E5	Heavy	CDR1	102	GFDFSKDWMS
25E5	Heavy	CDR2	103	EINPDSSTIN
25E5	Heavy	CDR3	104	SRLEDYEDWYFDV
25E6	Light	CDR1	105	KASQSVSNAVA
25E6	Light	CDR2	106	YTSNRYT
25E6	Light	CDR3	107	QQDYTSPWT
25E6	Heavy	CDR1	108	GYTFNTYNMY
25E6	Heavy	CDR2	109	GIDPSNGDTK
25E6	Heavy	CDR3	110	TSHTY
25E9	Light	CDR1	111	RSTKSLLHSNGNTYLY
25E9	Light	CDR2	112	RMSNLAS

Antibody designation	Chain type	CDR	SEQ ID NO:	Amino acid sequence
25E9	Light	CDR3	113	MQHLEYPFT
25E9	Heavy	CDR1	114	GYTFTDYDMH
25E9	Heavy	CDR2	115	TIDPETGGTA
25E9	Heavy	CDR3	116	TSFYYTYSNYDVGFAY
25B02	Light	CDR1	173	RASENIYSYLA
25B02	Light	CDR2	174	NAKTLPE
25B02	Light	CDR3	175	HHYGVPLT
25B02	Heavy	CDR1	176	GYTFTRNWIQ
25B02	Heavy	CDR2	177	AIYPGNGDSR
25B02	Heavy	CDR3	178	ARLAGNYAYYFDY
25D11	Light	CDR1	179	RASGNIHNYLA
25D11	Light	CDR2	180	NAKTLPE
25D11	Light	CDR3	181	QHHYGVPLT
25D11	Heavy	CDR1	182	GYTFTRNWIQ
25D11	Heavy	CDR2	183	AIYPGNGDSR
25D11	Heavy	CDR3	184	ARLAGNYAYYFDY
25E10	Light	CDR1	185	RASGNIHNYLA
25E10	Light	CDR2	186	NAKTLAD
25E10	Light	CDR3	187	QHHYGAPLT
25E10	Heavy	CDR1	188	GYTFTRNWIQ
25E10	Heavy	CDR2	189	AVYPGNGDSR
25E10	Heavy	CDR3	190	ARLAGNYAYYFDY

In certain embodiments of the present invention, the anti-Siglec-15 antibodies or antigen binding fragments may comprise the CDR sequences shown in Table 3 or have substantial sequence identity to the CDR sequences of Table 3. In an exemplary embodiment, the 25A1 anti-Siglec-15 antibody may comprise a light chain variable region containing CDR1, 2, and 3 that are encoded by SEQ ID NOS:68, 69, and 70, respectively, and/or a heavy chain variable region containing CDR1, 2, and 3 that are encoded by SEQ ID NOS:71, 72, and 73, respectively. In other embodiments the CDR3 region may be sufficient to provide antigen binding. As such polypeptides comprising the CDRL3 or the CDRH3 or both the CDRL3 and the CDRH3 are encompassed by the present invention.

Additionally, the anti-Siglec-15 antibodies or antigen binding fragments may include any combination of the CDRs listed in Table 3. For example, the antibodies or antigen binding fragments may include the light chain CDR3 and the heavy chain CDR3. It is understood that the CDRs that are contained in the anti-Siglec-15 antibodies or antigen binding fragments may be variant CDRs with 80%, 85%, 90%,

or 95% sequence identity to the CDR sequences presented in Table 3. Those skilled in the art will also recognize that the variants may include conservative amino acid changes, amino acid substitutions, deletions, or additions in the CDR sequences listed in Table 3.

Other exemplary embodiments of the invention include an isolated antibody or antigen binding fragment capable of specific binding to SEQ ID NO:2 or to a variant thereof (a variant having at least 80% identity with amino acids 20 to 259 or with amino acids 49-165 of SEQ ID NO. :2), the antibody comprising:

a. the 3 CDRs of a light chain variable domain listed in Table 5B and the 3 CDRs of a heavy chain variable listed in Table 5A;
b. the 3 CDRs of a light chain variable domain defined in SEQ ID NO.:194 and the 3 CDRs of a heavy chain variable domain defined in SEQ ID NO.:191;
c. the 3 CDRs of a light chain variable domain defined in SEQ ID NO.:195 and the 3 CDRs of a heavy chain variable domain defined in SEQ ID NO.:192;
d. the 3 CDRs of a light chain variable domain defined in SEQ ID NO.:196 and the 3 CDRs of a heavy chain variable domain defined in SEQ ID NO.:193;
e. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:38 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:40;
f. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:42 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:44;
g. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:46 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:48;
h. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:50 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:52
i. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:54 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:56;

j. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:58 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:60;

k. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:62 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:64;

l. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:66 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:68;

m. the 3 CDRs of a light chain variable domain defined in SEQ ID NO.:162 and the 3 CDRs of a heavy chain variable domain defined in SEQ ID NO.:164,

n. the 3 CDRs of a light chain variable domain defined in SEQ ID NO.:166 and the 3 CDRs of a heavy chain variable domain defined in SEQ ID NO.:168, or;

o. the 3 CDRs of a light chain variable domain defined in SEQ ID NO.:170 and the 3 CDRs of a heavy chain variable domain defined in SEQ ID NO.:172.

In an additional aspect, the present invention relates to an isolated antibody or antigen binding fragment capable of specific binding to Siglec-15 or to a variant thereof (a variant having at least 80% identity with amino acids 20 to 259 or with amino acids 49-165 of SEQ ID NO. :2), the antibody comprising:

a) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with the sequence listed in Table 5B and heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with the sequence listed in Table 5A;

b) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:194 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:191;

c) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:195 and a

heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:192;

d) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:196 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:193;

e) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:38 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:40,

f) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:42 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:44;

g) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:46 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:48;

h) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:50 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:52;

i) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:54 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:56;

j) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:58 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:60;

k) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:62 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:64,

l) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:66 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:68,

m) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:162 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:164,

n) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:166 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:168, and;

o) a light chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:170 and a heavy chain variable domain having at least 70% (75%, 80%, 85%, 90%, 95%, 100%) sequence identity with SEQ ID NO.:172.

Again, the light chain variable region of the specific combination provided above may be changed for any other light chain variable region described herein. Similarly, the heavy chain variable region of the specific combination provided above may be changed for any other heavy chain variable region described herein.

Variant antibody and antigen binding fragments

The present invention also encompasses variants of the antibodies or antigen binding fragments described herein. Variant antibodies or antigen binding fragments included are those having a variation in the amino acid sequence. For example, variant antibodies or antigen binding fragments included are those having at least one variant CDR (two, three, four, five, six and up to twelve variant CDRs), a variant light chain variable domain, a variant heavy chain variable domain, a variant light chain and/or a variant heavy chain. Variant antibodies or antigen binding fragments included in the present invention are those having, for example, similar or improved binding affinity in comparison with the original antibody or antigen binding fragment.

As used herein the term "variant" applies to any of the sequence described herein and includes for example, a variant CDR (either CDRL1, CDRL2, CDRL3,

CDRH1, CDRH2 and/or CDRH3), a variant light chain variable domain, a variant heavy chain variable domain, a variant light chain, a variant heavy chain, a variant antibody, a variant antigen binding fragment and a SEQ ID NO.:2 variant.

Variant antibodies or antigen binding fragments encompassed by the present invention are those which may comprise an insertion, a deletion or an amino acid substitution (conservative or non-conservative). These variants may have at least one amino acid residue in its amino acid sequence removed and a different residue inserted in its place.

The sites of greatest interest for substitutional mutagenesis include the hypervariable regions (CDRs), but modifications in the framework region or even in the constant region are also contemplated. Conservative substitutions may be made by exchanging an amino acid (of a CDR, variable chain, antibody, etc.) from one of the groups listed below (group 1 to 6) for another amino acid of the same group.

Generally, mutations in the CDRs may have a greater impact on the antigen binding activity of the antibody or antigen binding fragment than mutations in the framework region. Variant antibody or antigen binding fragments that are encompassed by the present invention are those which have a substantially identical antigen binding capacity (including similar, identical, or slightly less) to those presented herein or have a better antigen binding capacity than those presented herein.

Other exemplary embodiment of conservative substitutions are shown in **Table 1A** under the heading of "preferred substitutions". If such substitutions result in a undesired property, then more substantial changes, denominated "exemplary substitutions" in **Table 1A**, or as further described below in reference to amino acid classes, may be introduced and the products screened.

It is known in the art that variants may be generated by substitutional mutagenesis and retain the biological activity of the polypeptides of the present invention. These variants have at least one amino acid residue in the amino acid sequence removed and a different residue inserted in its place. For example, one site of interest for substitutional mutagenesis may include a site in which particular residues obtained from various species are identical. Examples of substitutions identified as “conservative substitutions” are shown in **Table 1A**. If such substitutions result in a change not desired, then other type of substitutions, denominated

"exemplary substitutions" in **Table 1A**, or as further described herein in reference to amino acid classes, are introduced and the products screened.

Substantial modifications in function or immunological identity are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation. (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side chain properties:

(group 1) hydrophobic: norleucine, methionine (Met), Alanine (Ala), Valine (Val), Leucine (Leu), Isoleucine (Ile)

(group 2) neutral hydrophilic: Cysteine (Cys), Serine (Ser), Threonine (Thr)

(group 3) acidic: Aspartic acid (Asp), Glutamic acid (Glu)

(group 4) basic: Asparagine (Asn), Glutamine (Gln), Histidine (His), Lysine (Lys), Arginine (Arg)

(group 5) residues that influence chain orientation: Glycine (Gly), Proline (Pro); and

(group 6) aromatic: Tryptophan (Trp), Tyrosine (Tyr), Phenylalanine (Phe)

Non-conservative substitutions will entail exchanging a member of one of these classes for another.

Table 1A. Amino acid substitution

Original residue	Exemplary substitution	Conservative substitution
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln, His, Lys, Arg, Asp	Gln
Asp (D)	Glu, Asn	Glu
Cys (C)	Ser, Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp, Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn, Gln, Lys, Arg,	Arg

Original residue	Exemplary substitution	Conservative substitution
Ile (I)	Leu, Val, Met, Ala, Phe, norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Leu, Met, Phe, Ala, norleucine	Leu

Variation in the amino acid sequence of the variant antibody or antigen binding fragment may include an amino acid addition, deletion, insertion, substitution etc., one or more modification in the backbone or side-chain of one or more amino acid, or an addition of a group or another molecule to one or more amino acids (side-chains or backbone).

Variant antibody or antigen binding fragment may have substantial sequence similarity and/or sequence identity in its amino acid sequence in comparison with that of the original antibody or antigen binding fragment amino acid sequence. The degree of similarity between two sequences is based upon the percentage of identities (identical amino acids) and of conservative substitution.

Generally, the degree of similarity and identity between variable chains has been determined herein using the Blast2 sequence program (Tatiana A. Tatusova, Thomas L. Madden (1999), "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences", FEMS Microbiol Lett. 174:247-250) using default settings, i.e., blastp program, BLOSUM62 matrix (open gap 11 and extension gap penalty 1; gapx dropoff 50, expect 10.0, word size 3) and activated filters.

Percent identity will therefore be indicative of amino acids which are identical in comparison with the original peptide and which may occupy the same or similar position.

Percent similarity will be indicative of amino acids which are identical and those which are replaced with conservative amino acid substitution in comparison with the original peptide at the same or similar position.

Variants (i.e.,analogues) of the present invention (including VL variants, VH variants, CDR variants, antibody variants, polypeptide variants, etc.) therefore comprise those which may have at least 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with an original sequence or a portion of an original sequence.

In accordance with the present invention, a SEQ ID NO.:2 variant includes a polypeptide having a region at least 80% identical with amino acids 49-165 or with amino acids 20 to 259 of SEQ ID NO.:2. Variants of SEQ ID NO.:2 also include polypeptides having at least 80% sequence identity with SEQ ID NO.:2.

Exemplary embodiments of variants are those having at least 81% sequence identity to a sequence described herein and 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Other exemplary embodiments of variants are those having at least 82% sequence identity to a sequence described herein and 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Further exemplary embodiments of variants are those having at least 85% sequence identity to a sequence described herein and 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Other exemplary embodiments of variants are those having at least 90% sequence identity to a sequence described herein and 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Additional exemplary embodiments of variants are those having at least 95% sequence identity to a sequence described herein and 95%, 96%, 97%, 98%, 99% or

100% sequence similarity with an original sequence or a portion of an original sequence.

Yet additional exemplary embodiments of variants are those having at least 97% sequence identity to a sequence described herein and 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

For a purpose of concision the applicant provides herein a Table 1B illustrating exemplary embodiments of individual variants encompassed by the present invention and comprising the specified % sequence identity and % sequence similarity. Each "X" is to be construed as defining a given variant.

Table 1B

Percent (%) sequence similarity	Percent (%) sequence identity																				
	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
80	X																				
81	X	X																			
82	X	X	X																		
83	X	X	X	X																	
84	X	X	X	X	X																
85	X	X	X	X	X	X															
86	X	X	X	X	X	X	X														
87	X	X	X	X	X	X	X	X													
88	X	X	X	X	X	X	X	X	X												
89	X	X	X	X	X	X	X	X	X	X											
90	X	X	X	X	X	X	X	X	X	X	X										
91	X	X	X	X	X	X	X	X	X	X	X	X									
92	X	X	X	X	X	X	X	X	X	X	X	X	X								
93	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
94	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
95	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
96	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
97	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
98	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
99	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
100	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

As used herein, the term "identical" means that a sequence share 100% sequence identity with another sequence.

As used herein, the term "substantially identical" means that a sequence share 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity with another sequence or a portion of another sequence.

The present invention encompasses CDRs, light chain variable domains, heavy chain variable domains, light chains, heavy chains, antibodies and/or antigen

binding fragments which comprise at least 80% identity with the sequence described herein.

Exemplary embodiments of the antibody or antigen binding fragment of the present invention are those comprising a light chain variable domain comprising a sequence selected from the group consisting of a sequence at least 70% identical (including 80%, 85%, 90%, 95% and 100% identical) to SEQ ID NO.:38, a sequence at least 70% identical (including 80%, 85%, 90%, 95% and 100% identical) to SEQ ID NO.:42, a sequence at least 70% identical (including 80%,85%, 90%, 95% and 100% identical) to SEQ ID NO.:46, a sequence at least 70% identical (including 80%,85%, 90%, 95% and 100% identical) to SEQ ID NO.:50, a sequence at least 70% identical (including 80%,85%, 90%, 95% and 100% identical) to SEQ ID NO.:54, a sequence at least 70% identical (including 80%, 85%, 90%, 95% and 100%) identical to SEQ ID NO.:58, a sequence at least 70% identical (including 80%, 85%, 90%, 95% and 100% identical) to SEQ ID NO.:62, a sequence 70% identical (including at least 80%, 85%, 90%, 95% and 100% identical) to SEQ ID NO.:66, a sequence 70% identical (including at least 80%, 85%, 90%, 95% and 100% identical) to SEQ ID NO.:162, a sequence 70% identical (including at least 80%, 85%, 90%, 95% and 100% identical) to SEQ ID NO.:166 and a sequence 70% identical (including at least 80%, 85%, 90%, 95% and 100% identical) to SEQ ID NO.:170.

These light chain variable domain may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO:69, a CDRL2 sequence at least 80 % identical to SEQ ID NO: 70 and a CDRL3 sequence at least 80 % identical to SEQ ID NO: 71.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO:69.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO:69.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence at least 90 % identical to SEQ ID NO: 70.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 70.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 71.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO: 71.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO: 75, a CDRL2 sequence at least 80 % identical to SEQ ID NO: 76 and a CDRL3 sequence at least 80 % identical to SEQ ID NO: 77.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 75.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 75.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a the CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 76.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 76.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 77.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO: 77.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO: 81, a CDRL2 sequence at least 80

% identical to SEQ ID NO: 82 and a CDRL3 sequence at least 80 % identical to SEQ ID NO: 83.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 81.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 81.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a the CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 82.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 82.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 83.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO: 83.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO: 87, a CDRL2 sequence at least 80 % identical to SEQ ID NO: 88 and a CDRL3 sequence at least 80 % identical to SEQ ID NO: 89.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 87.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 87.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a the CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 88.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 88.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 89.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO: 89.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO: 93, a CDRL2 sequence at least 80 % identical to SEQ ID NO: 94 and a CDRL3 sequence at least 80 % identical to SEQ ID NO: 95.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 93.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 93.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a the CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 94.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 94.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 95.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO: 95.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO: 99, a CDRL2 sequence at least 80

% identical to SEQ ID NO: 100 and a CDRL3 sequence at least 80 % identical to SEQ ID NO: 101.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 99.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 99.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a the CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 100.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 100.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 101.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO: 101.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO: 105, a CDRL2 sequence at least 80 % identical to SEQ ID NO: 106 and a CDRL3 sequence at least 80 % identical to SEQ ID NO: 107.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 105.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 105.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 106.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 106.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 107.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO: 107.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO: 111, a CDRL2 sequence at least 80 % identical to SEQ ID NO: 112 and a CDRL3 sequence at least 80 % identical to SEQ ID NO: 113.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 111.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 111.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 112.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 112.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 113.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 100 % identical to SEQ ID NO: 113.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:173, a CDRL2 sequence at least 80

% identical to SEQ ID NO.:174 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:175.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 173.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 173.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 174

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 174.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 175.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 100 % identical to SEQ ID NO: 175.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:179, a CDRL2 sequence at least 80 % identical to SEQ ID NO.:180 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:181.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 179.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 179.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 180.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 180.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 181.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 100 % identical to SEQ ID NO: 181.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:185, a CDRL2 sequence at least 80 % identical to SEQ ID NO.:186 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:187.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO: 185.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO: 185.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO: 186.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO: 186.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO: 187.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 100 % identical to SEQ ID NO: 187.In an exemplary embodiment, the antibody or antigen binding fragment may comprise a heavy chain variable domain comprising a sequence selected from the group consisting of a sequence at least 70% identical (including 80%, 85%, 90%, 95%, 100% identical) to SEQ ID NO:40, a sequence at

least 70% identical (including 80% identical) to SEQ ID NO:44, a sequence at least 70% identical (including 80%, 85%, 90%, 95%, 100% identical) to SEQ ID NO:48, a sequence at least 70% identical (including 80%,85%, 90%, 95%, 100% identical) to SEQ ID NO:52, a sequence at least 70% identical (including 80%,85%, 90%, 95%, 100% identical) to SEQ ID NO:56, a sequence at least 70% identical (including 80%,85%, 90%, 95%, 100% identical) to SEQ ID NO:60, a sequence at least 70% identical (including 80%,85%, 90%, 95%, 100%) identical to SEQ ID NO:64, a sequence at least 70% identical (including 80%,85%, 90%, 95%, 100% identical) to SEQ ID NO:68, a sequence at least 70% identical (including 80%,85%, 90%, 95%, 100% identical) to SEQ ID NO:164, a sequence at least 70% identical (including 80%,85%, 90%, 95%, 100% identical) to SEQ ID NO:168 and a sequence at least 70% identical (including 80%,85%, 90%, 95%, 100% identical) to SEQ ID NO:172.

These heavy chain variable domain may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO:72, a CDRH2 sequence at least 80 % identical to SEQ ID NO:73 and a CDRH3 sequence at least 80 % identical to SEQ ID NO:74.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO:72.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO:72.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO:73.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO:73.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO:74.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO:74.

The heavy chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO:78, a CDRH2 sequence at least 80 % identical to SEQ ID NO:79 and a CDRH3 sequence at least 80 % identical to SEQ ID NO:80.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO:78.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO:78.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO:79.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO:79.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO:80.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO:80.

The light chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO: 84, a CDRH2 sequence at least 80 % identical to SEQ ID NO: 85 and a CDRH3 sequence at least 80 % identical to SEQ ID NO: 86.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO: 84.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO: 84.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO: 85.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO: 85.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO: 86.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO: 86.

The light chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO: 90, a CDRH2 sequence at least 80 % identical to SEQ ID NO: 91 and a CDRH3 sequence at least 80 % identical to SEQ ID NO: 92.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO: 90.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO: 90.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO: 91.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO: 91.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO: 92.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO: 92.

The light chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO: 96, a CDRH2 sequence at least 80 % identical to SEQ ID NO: 97 and a CDRH3 sequence at least 80 % identical to SEQ ID NO: 98.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO: 96.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO: 96.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO: 97.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO: 97.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO: 98.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO: 98.

The light chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO: 102, a CDRH2 sequence at least 80 % identical to SEQ ID NO: 103 and a CDRH3 sequence at least 80 % identical to SEQ ID NO: 104.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO: 102.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO: 102.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO: 103.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO: 103.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO: 104.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO: 104.

These heavy chain variable domain may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO:108, a CDRH2 sequence at least 80 % identical to SEQ ID NO:109 and a CDRH3 sequence at least 80 % identical to SEQ ID NO:110. In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO: 108.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO: 108.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO: 109.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO: 109.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO: 110.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO: 110.

These heavy chain variable domain may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO:114, a CDRH2 sequence at least 80 % identical to SEQ ID NO:115 and a CDRH3 sequence at least 80 % identical to SEQ ID NO:116.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO: 114.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO: 114.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO: 115.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO: 115.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO: 116.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO: 116.

These heavy chain variable domains may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:176, a CDRH2 sequence at least 80 % identical to SEQ ID NO.:177 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:178.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.: 176.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.: 176.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.: 177.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.: 177.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.: 178.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.: 178.

These heavy chain variable domains may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:182, a CDRH2 sequence at least 80 % identical to SEQ ID NO.:183 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:184.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.: 182.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.: 182.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.: 183.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.: 183.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.: 184.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.: 184.

These heavy chain variable domains may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:188, a CDRH2 sequence at least 80 % identical

to SEQ ID NO.:189 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:190.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.: 188.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.: 188.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.: 189.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.: 189.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.: 190.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.: 190.

Production of the antibodies in cells

The antibodies that are disclosed herein can be made by a variety of methods familiar to those skilled in the art, such as hybridoma methodology or by recombinant DNA methods.

In an exemplary embodiment of the invention, the antibodies may be produced by the conventional hybridoma technology, where a mouse is immunized with an antigen, spleen cells isolated and fused with myeloma cells lacking HGPRT expression and hybrid cells selected by hypoxanthine, aminopterin and thymine (HAT) containing media.

In an additional exemplary embodiment of the invention, the antibodies may be produced by recombinant DNA methods.

In order to express the antibodies, nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may be inserted

into an expression vector, i.e., a vector that contains the elements for transcriptional and translational control of the inserted coding sequence in a particular host. These elements may include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' un-translated regions. Methods that are well known to those skilled in the art may be used to construct such expression vectors. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination.

A variety of expression vector/host cell systems known to those of skill in the art may be utilized to express a polypeptide or RNA derived from nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with baculovirus vectors; plant cell systems transformed with viral or bacterial expression vectors; or animal cell systems. For long-term production of recombinant proteins in mammalian systems, stable expression in cell lines may be effected. For example, nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may be transformed into cell lines using expression vectors that may contain viral origins of replication and/or endogenous expression elements and a selectable or visible marker gene on the same or on a separate vector. The invention is not to be limited by the vector or host cell employed. In certain embodiments of the present invention, the nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may each be ligated into a separate expression vector and each chain expressed separately. In another embodiment, both the light and heavy chains able to encode any one of a light and heavy immunoglobulin chains described herein may be ligated into a single expression vector and expressed simultaneously.

Alternatively, RNA and/or polypeptide may be expressed from a vector comprising nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein using an *in vitro* transcription system or a coupled *in vitro* transcription/translation system respectively.

In general, host cells that contain nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein and/or that express a polypeptide encoded by the nucleotide sequences able to encode any one of a light

and heavy immunoglobulin chains described herein, or a portion thereof, may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA/DNA or DNA/RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques that include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or amino acid sequences. Immunological methods for detecting and measuring the expression of polypeptides using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). Those of skill in the art may readily adapt these methodologies to the present invention.

Host cells comprising nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may thus be cultured under conditions for the transcription of the corresponding RNA (mRNA, siRNA, shRNA etc.) and/or the expression of the polypeptide from cell culture. The polypeptide produced by a cell may be secreted or may be retained intracellularly depending on the sequence and/or the vector used. In an exemplary embodiment, expression vectors containing nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may be designed to contain signal sequences that direct secretion of the polypeptide through a prokaryotic or eukaryotic cell membrane.

Due to the inherent degeneracy of the genetic code, other DNA sequences that encode the same, substantially the same or a functionally equivalent amino acid sequence may be produced and used, for example, to express a polypeptide encoded by nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein. The nucleotide sequences of the present invention may be engineered using methods generally known in the art in order to alter the nucleotide sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed polypeptide in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. In an exemplary embodiment, antibodies that contain particular glycosylation structures or patterns may be desired. Post-translational processing, which cleaves a "prepro" form of the polypeptide, may also be used to specify protein targeting, folding, and/or activity. Different host cells that have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and W138) are available commercially and from the American Type Culture Collection (ATCC) and may be chosen to ensure the correct modification and processing of the expressed polypeptide.

Since hybridoma cells are hybrid mouse cells, they are strictly used to produce murine antibodies. It is clear that the glycosyl side chains of such murine antibodies might significantly differ from the glycosylation pattern observed in human cells. Differences in phosphorylation pattern between human cells and hybridomas might also have an impact on the activity of the antibody. Furthermore, administration of murine antibodies to human usually induces an anti-antibody immune response that could potentially neutralize any of the biological activity that the murine antibody might have.

In order to minimize recognition of murine antibodies by the human immune system or for improving the biological activity of the antibodies in human, murine antibodies are advantageously converted into partially (e.g., chimeric) or fully humanized antibodies. Recombinant form of the light chain and heavy chain of the (partially or fully) humanized antibody may thus be introduced into a mammalian expression system other than hybridoma cells (such as 293 cells, CHO or else). Mammalian expression system may procure the advantage of having a resulting glycosylation pattern that is closer to that of naturally occurring human form of the antibodies.

For example, in the case of lytic IgG1 antibodies, the proper glycosylation of the immunoglobulin chains is necessary for effector functions. These biological functions of IgG1 monoclonal antibodies include antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), both of which will be greatly

influenced by the type of glycosyl side chains that are grafted to the amino acids during expression in mammalian cells.

In addition, optimized mammalian cell expression systems will often secrete significantly a greater amounts of antibodies compared to hybridomas. Therefore, there is a practical and probably economical reason for adopting human cells for production.

Those of skill in the art will readily appreciate that natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence resulting in translation of a fusion polypeptide containing heterologous polypeptide moieties in any of the aforementioned host systems. Such heterologous polypeptide moieties may facilitate purification of fusion polypeptides using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein, thioredoxin, calmodulin binding peptide, 6-His (His), FLAG, c-myc, hemaglutinin (HA), and antibody epitopes such as monoclonal antibody epitopes.

In yet a further aspect, the present invention relates to a polynucleotide which may comprise a nucleotide sequence encoding a fusion protein. The fusion protein may comprise a fusion partner (e.g., HA, Fc, etc.) fused to the polypeptide (e.g., complete light chain, complete heavy chain, variable regions, CDRs etc.) described herein.

Those of skill in the art will also readily recognize that the nucleic acid and polypeptide sequences may be synthesized, in whole or in part, using chemical or enzymatic methods well known in the art. For example, peptide synthesis may be performed using various solid-phase techniques and machines such as the ABI 431A Peptide synthesizer (PE Biosystems) may be used to automate synthesis. If desired, the amino acid sequence may be altered during synthesis and/or combined with sequences from other proteins to produce a variant protein.

Antibody conjugates

Although it is not always necessary, for detection or therapeutic purposes, the antibody or antigen binding fragment of the present invention may be conjugated with a detectable moiety (i.e., for detection or diagnostic purposes) or with a therapeutic moiety (for therapeutic purposes).

For detection purposes, an unconjugated antibody (primary antibody) may be used for binding to the antigen and a secondary antibody carrying a detectable moiety and capable of binding to the primary antibody may be added. However, as indicated above, the anti-SIGLEC 15 antibody may be conjugated with a detectable label and as such a secondary antibody may not be necessary,

A "detectable moiety" is a moiety detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical and/or other physical means. A detectable moiety may be coupled either directly and/or indirectly (for example via a linkage, such as, without limitation, a DOTA or NHS linkage) to antibodies and antigen binding fragments thereof of the present invention using methods well known in the art. A wide variety of detectable moieties may be used, with the choice depending on the sensitivity required, ease of conjugation, stability requirements and available instrumentation. A suitable detectable moiety include, but is not limited to, a fluorescent label, a radioactive label (for example, without limitation, ^{125}I, In^{111}, Tc^{99}, I^{131} and including positron emitting isotopes for PET scanner etc), a nuclear magnetic resonance active label, a luminiscent label, a chemiluminescent label, a chromophore label, an enzyme label (for example and without limitation horseradish peroxidase, alkaline phosphatase, etc.), quantum dots and/or a nanoparticle. Detectable moiety may cause and/or produce a detectable signal thereby allowing for a signal from the detectable moiety to be detected.

In another exemplary embodiment of the invention, the antibody or antigen binding fragment thereof may be coupled (modified) with a therapeutic moiety (e.g., drug, cytotoxic moiety).

In some instances, for therapeutic purposes, an unconjugated antibody may by itself be capable of sequestering the antigen, may block an important interaction between the antigen and another binding partner, may recruit effector cells, etc. However, as indicated above, the antibody may be conjugated with a therapeutic moiety.

In an exemplary embodiment, the antibodies and antigen binding fragments may comprise a chemotherapeutic or cytotoxic agent. For example, the antibody and antigen binding fragments may be conjugated to the chemotherapeutic or cytotoxic agent. Such chemotherapeutic or cytotoxic agents include, but are not limited to, Yttrium-90, Scandium-47, Rhenium-186, Iodine-131, Iodine-125, and many others recognized by those skilled in the art (e.g., lutetium (e.g., Lu^{177}), bismuth (e.g., Bi^{213}),

copper (e.g., Cu^{67})). In other instances, the chemotherapeutic or cytotoxic agent may be comprised of, among others known to those skilled in the art, 5-fluorouracil, adriamycin, irinotecan, taxanes, pseudomonas endotoxin, ricin and other toxins.

Alternatively, in order to carry out the methods of the present invention and as known in the art, the antibody or antigen binding fragment of the present invention (conjugated or not) may be used in combination with a second molecule (e.g., a secondary antibody, etc.) which is able to specifically bind to the antibody or antigen binding fragment of the present invention and which may carry a desirable detectable, diagnostic or therapeutic moiety.

Pharmaceutical compositions of the antibodies and their use

Pharmaceutical compositions of the antibodies (conjugated or not) are also encompassed by the present invention. The pharmaceutical composition may comprise an antibody or an antigen binding fragment and may also contain a pharmaceutically acceptable carrier.

Other aspects of the invention relate to a composition which may comprise the antibody or antigen binding fragment described herein and a carrier.

Yet other aspects of the invention relate to the use of the isolated antibody or antigen binding fragment described herein in the treatment or diagnosis of bone diseases or cancer.

In addition to the active ingredients, a pharmaceutical composition may contain pharmaceutically acceptable carriers comprising water, PBS, salt solutions, gelatins, oils, alcohols, and other excipients and auxiliaries that facilitate processing of the active compounds into preparations that may be used pharmaceutically. In other instances, such preparations may be sterilized.

As used herein, "pharmaceutical composition" usually comprises therapeutically effective amounts of the agent together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers. A "therapeutically effective amount" as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen. Such compositions are liquids or lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCl., acetate, phosphate), pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts). Solubilizing

agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the protein, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, hydrogels, etc, or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils). Also comprehended by the invention are particulate compositions coated with polymers (e.g., poloxamers or poloxamines). Other embodiments of the compositions of the invention incorporate particulate forms protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal, oral, vaginal, rectal routes. In one embodiment the pharmaceutical composition is administered parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitonealy, intraventricularly, intracranially and intratumorally.

Further, as used herein "pharmaceutically acceptable carrier" or "pharmaceutical carrier" are known in the art and include, but are not limited to, 0.01-0.1 M or 0.05 M phosphate buffer or 0.8 % saline. Additionally, such pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's orfixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, collating agents, inert gases and the like.

For any compound, the therapeutically effective dose may be estimated initially either in cell culture assays or in animal models such as mice, rats, rabbits,

dogs, or pigs. An animal model may also be used to determine the concentration range and route of administration. Such information may then be used to determine useful doses and routes for administration in humans. These techniques are well known to one skilled in the art and a therapeutically effective dose refers to that amount of active ingredient that ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating and contrasting the ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population) statistics. Any of the therapeutic compositions described above may be applied to any subject in need of such therapy, including, but not limited to, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and humans.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

The term "treatment" for purposes of this disclosure refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

The antibodies or antigen binding fragments may have therapeutic uses in the treatment of various bone loss or cancer. In an exemplary embodiment, the antibodies or fragments may have therapeutic uses in bone loss associated with bone diseases such as conditions where there is an increase in the bone degradative activity of osteoclasts. In certain instances, the antibodies or antigen binding fragments may interact with cells that express SEQ ID NO:2 and induce an immunological reaction by mediating ADCC. In other instances, the antibodies and fragments may block the interaction of SEQ ID NO:2 with its protein partners.

The anti-Siglec-15 antibodies or antigen binding fragments may have therapeutic uses in the treatment of bone loss in the context of various bone-related diseases, including but not limited to osteoporosis, osteopenia, osteomalacia, hyperparathyroidism, hypothyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia,

hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's disease/syndrome, Tumer syndrome, Gaucher disease, Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, periodontal disease, rickets (including vitamin D dependent, type I and II, and x-linked hypophosphatemic rickets), fibrogenesis imperfecta ossium, osteosclerotic disorders such as pycnodysostosis and damage caused by macrophage-mediated inflammatory processes. In the preferred embodiment, the antibodies and fragments have therapeutic uses in conditions where severe bone loss prevails, in particular metastatic cancer to the bone. In certain instances, the anti-Siglec-15 antibodies and fragments may interact with cells, such as osteoclasts, that express Siglec-15. In other instances, the anti-Siglec-15 antibodies and fragments may block the interaction of Siglec-15 with its protein partners.

The anti-Siglec-15 antibodies and antigen binding fragments thereof may have therapeutic uses in the treatment of cancer or bone loss caused by or associated with various bone remodelling disorders. In particular, the anti-Siglec-15 antibodies and immunologically functional fragments therein have therapeutic uses in conditions where osteoclasts are hyperactive and contribute to the degradation of the bone surface. In certain instances, the anti-Siglec-15 antibodies and antigen binding fragment thereof may be administered concurrently in combination with other treatments given for the same condition. As such, the antibodies may be administered with anti-resorptives (e.g., bisphosphonates) that are known to those skilled in the art. Additionally, the antibodies may be administered with anti-mitotics (e.g., taxanes), platinum-based agents (e.g., cisplatin), DNA damaging agents (e.g. Doxorubicin), and other cytotoxic therapies that are known to those skilled in the art. In other instances, the anti-Siglec-15 antibodies and immunologically functional fragments therein may be administered with other therapeutic antibodies. These include, but are not limited to, antibodies that target RANKL, EGFR, CD-20, and Her2.

In certain instances, the antibodies and antigen binding fragments therein may be administered concurrently in combination with other treatments given for the same condition. As such, the antibodies may be administered with anti-mitotics (e.g., taxanes), platinum-based agents (e.g., cisplatin), DNA damaging agents (e.g. Doxorubicin), and other anti-cancer therapies that are known to those skilled in the

art. In other instances, the antibodies and antigen binding fragments therein may be administered with other therapeutic antibodies. These include, but are not limited to, antibodies that target EGFR, CD-20, and Her2.

The present invention relates in a further aspect thereof to a method for inhibiting the growth of a SEQ ID NO:2-expressing cell or of SEQ ID NO:2 variant-expressing cell, the method which may comprise contacting the cell with an effective amount of the antibody or antigen binding fragment described herein.

The present invention also encompasses method of treating cancer or bone loss or inhibiting the growth of a SEQ ID NO:2 expressing cells or of SEQ ID NO:2 variant-expressing cell in a mammal, the method may comprise administering the antibody or antigen binding fragment described herein to a mammal in need.

The present invention also provides a method for inhibiting the growth of a cancer cell selected from the group consisting of ovarian cancer cells, renal cancer cells, cancer cells of the central nervous system, prostate cancer cells, melanoma cells, breast cancer cells, lung cancer cells or colon cancer cells. The method may comprise providing the cancer cell with a nucleic acid capable of impairing the expression of a polypeptide at least 80% identical to SEQ ID NO.:2 or having a region at least 80% identical to amino acids 20 to 259 or to amino acids 49 to 165 of SEQ ID NO.:2. The cancer cell may express a polypeptide at least 80% identical to SEQ ID NO.:2 or having a region at least 80% identical to amino acids 20 to 259 or to amino acids 49 to 165 of SEQ ID NO.:2.

In accordance with the present invention, the nucleic acid may be, for example, a siRNA or an antisense.

The present invention also encompasses method of detecting cancer or bone loss or detecting a SEQ ID NO:2-expressing cell or a SEQ ID NO:2 variant-expressing cell in a mammal, the method may comprise administering the antibody or antigen binding fragment described herein to a mammal in need.

The present invention relates in another aspect thereof to a method for detecting a SEQ ID NO:2-expressing cell or a SEQ ID NO:2 variant-expressing cell, the method may comprise contacting the cell with an antibody or antigen binding fragment described herein and detecting a complex formed by the antibody and the SEQ ID NO:2-expressing cell or the SEQ ID NO:2 variant-expressing cell.

Another aspect of the invention relates to a method for detecting SEQ ID NO:2, a variant having at least 80% sequence identity with amino acids 20-259 or

with amino acids 49-165 of SEQ ID NO:2, the method may comprise contacting a cell expressing SEQ ID NO:2 or the variant or a sample (biopsy, serum, plasma, urine etc.) comprising or suspected of comprising SEQ ID NO:2 or the variant with the antibody or antigen binding fragments described herein and measuring binding.

The binding of an antibody to an antigen will cause an increase in the expected molecular weight of the antigen. A physical change therefore occurs upon specific binding of the antibody or antigen binding fragment and the antigen.

Such changes may be detected using, for example, electrophoresis followed by Western blot and coloration of the gel or blot, mass spectrometry, HPLC coupled with a computer or else. Apparatus capable of computing a shift in molecular weight are known in the art and include for example, Phosphorimager™.

When the antibody comprises for example a detectable label, the antigen-antibody complex may be detected by the fluorescence emitted by the label, radiation emission of the label, enzymatic activity of a label provided with its substrate or else.

Detection and/or measurement of binding between an antibody or antigen binding fragment and an antigen may be performed by various methods known in the art. Binding between an antibody or antigen binding fragment and an antigen may be monitored with an apparatus capable of detecting the signal emitted by the detectable label (radiation emission, fluorescence, color change etc.). Such apparatus provides data which indicates that binding as occurred and may also provide indication as to the amount of antibody bound to the antigen. The apparatus (usually coupled with a computer) may also be capable of calculating the difference between a background signal (e.g., signal obtained in the absence of antigen-antibody binding) or background noise and the signal obtained upon specific antibody-antigen binding. Such apparatuses may thus provide the user with indications and conclusions as to whether the antigen has been detected or not.

The sample may originate from a mammal (e.g., a human) which may have cancer or bone disease or may be suspected of having cancer or a bone disease or may experience bone loss or may be subject of experiencing bone loss. The sample may be a tissue sample obtained from the mammal or a cell culture supernatant.

In accordance with the invention the sample may be a serum sample, a plasma sample, a blood sample or ascitic fluid obtained from the mammal. The antibody or antigen binding fragment described herein may advantageously detect SEQ ID NO:2.

The method may comprise quantifying the complex formed by the antibody or antigen binding fragment bound to SEQ ID NO:2 or to the SEQ ID NO:2 variant.

The antibody or antigen binding fragment of the present invention may more particularly be used in the detection, diagnosis or treatment of bone disease or cancer.

Additional aspects of the invention relates to kits which may include one or more container containing one or more antibodies or antigen binding fragments described herein.

Nucleic acids, vectors and cells

Antibodies are usually made in cells allowing expression of the light chain and heavy chain expressed from a vector(s) comprising a nucleic acid sequence encoding the light chain and heavy chain.

The present therefore encompasses nucleic acids capable of encoding any of the CDRs (including CDR variants), light chain variable domains (including light chain variable domain variants), heavy chain variable domains (including heavy chain variable domain variants), light chains (including light chain variants), heavy chains (including heavy chain variants) described herein.

Exemplary embodiments of nucleic acids of the present invention include nucleic acids encoding a light chain variable domain comprising:

a. a CDRL1 sequence selected from the group consisting of SEQ ID NO:69, SEQ ID NO:75, SEQ ID NO:81, SEQ ID NO:87, SEQ ID NO:93, SEQ ID NO:99, SEQ ID NO:105 and SEQ ID NO:111;
b. a CDRL2 sequence selected from the group consisting of SEQ ID NO:70, SEQ ID NO:76. SEQ ID NO:82. SEQ ID NO:88. SEQ ID NO:94, SEQ ID NO:100, SEQ ID NO:106 and SEQ ID NO:112, and/or;
c. a CDRL3 sequence selected from the group consisting of SEQ ID NO:71, SEQ ID NO:77, SEQ ID NO:83, SEQ ID NO:89, SEQ ID NO:95, SEQ ID NO:101, SEQ ID NO:107 and SEQ ID NO:113.

In accordance with the present invention, the nucleic acid may encode a light chain variable domain which may comprise at least two CDRs of a CDRL1, a CDRL2 or a CDRL3.

Also in accordance with the present invention, the nucleic acid may encode a light chain variable domain which may comprise one CDRL1, one CDRL2 and one CDRL3.

The present invention also relates to a nucleic acid encoding a heavy chain variable domain comprising:

a. a CDRH1 sequence selected from the group consisting of SEQ ID NO:72, SEQ ID NO:78, SEQ ID NO:84, SEQ ID NO:90, SEQ ID NO:96, SEQ ID NO:102, SEQ ID NO:108 and SEQ ID NO:114;
b. a CDRH2 sequence selected from the group consisting of SEQ ID NO:73, SEQ ID NO:79, SEQ ID NO:85, SEQ ID NO:91, SEQ ID NO:97, SEQ ID NO:103, SEQ ID NO:109 and SEQ ID NO:115, and/or;
c. a CDRH3 sequence selected from the group consisting of SEQ ID NO:74, SEQ ID NO:80, SEQ ID NO:86, SEQ ID NO:92, SEQ ID NO:98, SEQ ID NO:104, SEQ ID NO:110 and SEQ ID NO:116.

In a further aspect, the present invention provides a nucleic acid encoding a light chain variable domain which may comprise:

a) a CDRL1 sequence selected from the group consisting of SEQ ID NO: 153, SEQ ID NO.:154, SEQ ID NO.:84, SEQ ID NO.:96 and SEQ ID NO.:102;
b) a CDRL2 sequence selected from the group consisting of SEQ ID NO: 149, SEQ ID NO.:150, SEQ ID NO.:76, SEQ ID NO.:82 and SEQ ID NO.:106, or;
c) a CDRL3 sequence selected from the group consisting of SEQ ID NO: 151, SEQ ID NO.:152, SEQ ID NO.:77, SEQ ID NO.:83, SEQ ID NO.:95, SEQ ID NO.:107 and SEQ ID NO.:152.

In yet a further aspect, the present invention provides a nucleic acid encoding a heavy chain variable domain which may comprise:

a) a CDRH1 sequence selected from the group consisting of SEQ ID NO: 153, SEQ ID NO.:154, SEQ ID NO.:84, SEQ ID NO.:96 and SEQ ID NO.:102;
b) a CDRH2 sequence selected from the group consisting of SEQ ID NO: 155, SEQ ID NO.:156, SEQ ID NO.:157, SEQ ID NO.:73, SEQ ID NO.:79, SEQ ID NO.:85, SEQ ID NO.:97, SEQ ID NO.:103 and SEQ ID NO.:109, or;

c) a CDRH3 sequence selected from the group consisting of SEQ ID NO: 158, SEQ ID NO.:74, SEQ ID NO.:98, SEQ ID NO.:104, SEQ ID NO.:110 and SEQ ID NO.:116.

In accordance with the present invention, the nucleic acid may encode a heavy chain variable domain which may comprise at least two CDRs of a CDRH1, a CDRH2 or a CDRH3.

In accordance with the present invention, the nucleic acid may encode a heavy chain variable domain which may comprise one CDRH1, one CDRH2 and one CDRH3.

Also encompassed by the present invention are nucleic acids encoding antibody variants having at least one conservative amino acid substitution.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution in at least two of the CDRs.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution in the 3 CDRs.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitution in at least one of the CDRs.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitution in at least two of the CDRs.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitution in the 3 CDRs.

Other aspects of the invention relate to a nucleic acid encoding a light chain variable domain having at least 70% (including at least 80%) sequence identity to a sequence selected from the group consisting of SEQ ID NO:37, SEQ ID NO.:41, SEQ ID NO.:45, SEQ ID NO.:49, SEQ ID NO.:53, SEQ ID NO.:57, SEQ ID NO.:61 and SEQ ID NO.:65.

Yet other aspects of the invention relate to a nucleic acid encoding a heavy chain variable domain having at least 70% (including at least 80%) sequence identity to a sequence selected from the group consisting of SEQ ID NO.:39, SEQ ID NO.:43,

SEQ ID NO.:47, SEQ ID NO.:51, SEQ ID NO.:55, SEQ ID NO.:59, SEQ ID NO.:63 and SEQ ID NO.:67.

In yet another aspect, the present invention relates to a vector comprising the nucleic acid described herein.

In accordance with the present invention, the vector may be an expression vector.

Vector that contains the elements for transcriptional and translational control of the inserted coding sequence in a particular host are known in the art. These elements may include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' un-translated regions. Methods that are well known to those skilled in the art may be used to construct such expression vectors. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination.

In another aspect the present invention relates to an isolated cell which may comprise the nucleic acid described herein.

The isolated cell may comprise a nucleic acid encoding a light chain variable domain and a nucleic acid encoding a heavy chain variable domain either on separate vectors or on the same vector. The isolated cell may also comprise a nucleic acid encoding a light chain and a nucleic acid encoding a heavy chain either on separate vectors or on the same vector.

In accordance with the present invention, the cell may be capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

In another aspect, the present invention provides a cell which may comprise and/or may express the antibody described herein.

In accordance with the invention, the cell may comprise a nucleic acid encoding a light chain variable domain and a nucleic acid encoding a heavy chain variable domain.

The cell may be capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

The examples below are presented to further outline details of the present invention.

Exemplary embodiments of screening assay

In an additional aspect the present invention provides methods of identifying a compound capable of inhibiting the growth of ovarian cancer cells, renal cancer cells, cancer cells of the central nervous system, prostate cancer cells, melanoma cells, breast cancer cells, lung cancer cells or colon cancer cells. The method may comprise providing a polypeptide comprising a region at least 80% identical to amino acids 20 to 259 of SEQ ID NO.:2 or a cell expressing said polypeptide with a candidate compound and measuring the activity or expression of the polypeptide. A reduced activity or expression of the polypeptide may positively identify a suitable inhibitory compound.

In accordance with the present invention, the candidate compound may specifically bind to the polypeptide.

In accordance with the present invention, the candidate compound may be, for example, an antibody or an antigen binding fragment.

In accordance with the present invention, the candidate compound may be, for example, a siRNA or an antisense.

Other types of assay may be carried out without departing from the scope of the invention.

EXAMPLES

Example 1

This example describes the pattern of expression of the *Siglec-15* gene in osteoclasts and human tissue RNA samples

One of the most promising genes identified was termed AB-0326, which encodes the cell surface type I membrane protein, Siglec-15. This candidate was first isolated from a human osteoclast library and a similar RANKL-dependent upregulation was also confirmed in primary mouse osteoclasts as well as the mouse RAW 264.7 cells compared to precursor cells by RT-PCR (Sooknanan et al. 2007). The tissue expression profile of Siglec-15 was assessed to determine the specificity of expression, a criteria that was imposed on all targets that were chosen for validation. Peripheral blood mononuclear cells (PBMNCs) were obtained from 6 human donors and cultured in osteoclast differentiation medium (MCS-F and RANKL) for at least 14 days. Total RNA was isolated from precursors cells (no RANKL treatment (Figure 1, top panel, -) or at intermediate time intervals (Figure 1, top panel, ◢). One microgram of each RNA sample was converted to single-

stranded cDNA using Thermoscript reverse transcriptase (Invitrogen, Burlington, ON) according to the manufacturer's instructions, diluted 200-fold, and used in a PCR reaction previously optimized to specifically amplify a fragment of the Siglec-15 transcript. The sequences of the oligonucleotides used in the PCR reaction are shown in SEQ ID NOS: 117 and 118. As shown in Figure 1 top panel, *differentiating osteoclasts*), the Siglec-15 transcript was either expressed at much lower level in the precursors cells compared to the differentiating osteoclasts. In addition, the level of Siglec-15 transcript increased as the differentiation progressed. By comparison, a known osteoclast marker gene, cathepsin K (CATK in Figure 1, *differentiating osteoclasts*) was also upregulated during osteoclast differentiation. The oligonucleotides used to amplify the CATK message are displayed in SEQ ID NOS: 119 and 120. As a control, PCR reactions were conducted on the same samples with primers that specifically amplify the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH, see lower panel of Figure 1, *differentiating osteoclasts*). The sequences of the GAPDH-specific primers used in the PCR reaction are shown in SEQ ID NOS: 121 and 122. This latter reaction demonstrates that an equal amount of starting RNA was present in each sample. Total RNA from human normal tissues was purchased from a commercial vendor (Clontech, Mountain View, CA) As shown in Figure 1 (upper panel, *Normal tissues*), Siglec-15 was weakly detected in a single tissue (lung, lane 9) and completely absent from all other tissue samples. This underscores the strength of the Applicant's discovery approach in its ability to identify targets that are highly restricted to differentiating osteoclasts. The lane numbers in Figure 1 correspond to the following tissues: The lanes correspond to the following tissues: lane 1, adrenal; 2, breast; 3, jejunum; 4, trachea; 5, liver; 6, placenta; 7, aorta; 8, brain; 9, lung; 10, adrenal cortex; 11, esophagus; 12, colon; 13, ovary; 14, kidney; 15, prostate; 16, thymus; 17, skeletal muscle; 18, vena cava; 19, stomach; 20, small intestine; 21, heart; 22, fallopian tube; 23, spleen; 24, bladder; 25, cervix; 26, pancreas; 27, ileum; 28, duodenum; 29, thyroid; 30, testicle; the blank lanes between lanes 10 and 11 and lanes 20 and 21 represent negative controls (no cDNA). Our results indicate that Siglec-15 is upregulated in differentiating osteoclasts, absent from virtually all normal human tissues and suggest that an antibody against Siglec-15 would interact significantly less with non-target tissues.

An additional expression profiling study was performed to determine the expression of Siglec-15 in cancer indications. One skilled in the art will recognize that

the antibodies described in this invention might have utilities in cancer if it was found that the *Siglec-15* gene was expressed in these types of indications. To address this, the PCR-based method was adapted to determine the expression pattern of the Siglec-15 transcript in cancer cell lines isolated from nine types of cancer. The cancer types represented by the cell lines are leukemia, central nervous system, breast, colon, lung, melanoma, ovarian, prostate, and renal cancer (see Table 4). These RNA samples were obtained from the Developmental Therapeutics Program at the NCI/NIH. Using the same RAMP RNA samples that was amplified from the total RNA samples obtained from the NCI, 500 ng of RNA was converted to single-stranded cDNA as described above. The cDNA reaction was diluted so that 1/200 of the reaction was used for each PCR experiment. PCR was conducted in 96-well plates using Hot-Start Taq Polymerase from Qiagen (Mississauga, ON) in a DNA Engine Tetrad from MJ Research. Half of the reaction mixture was loaded on a 1.2% agarose/ethidium bromide gel and the amplicons visualized with UV light. To verify that equal quantities of RNA was used in each reaction, the level of RNA was monitored with GAPDH expression.

Table 4 – List of cancer cell lines from the NCI-60 panel

Cell line	Cancer type
K-562	leukemia
MOLT-4	leukemia
CCRF-CEM	leukemia
RPMI-8226	leukemia
HL-60(TB)	leukemia
SR	leukemia
SF-268	CNS
SF-295	CNS
SF-539	CNS
SNB-19	CNS
SNB-75	CNS
U251	CNS
BT-549	breast
HS 578T	breast
MCF7	breast
NCI/ADR-RES	breast
MDA-MB-231	breast
MDA-MB-435	breast
T-47D	breast
COLO 205	colon
HCC-2998	colon

Cell line	Cancer type
HCT-116	colon
HCT-15	colon
HT29	colon
KM12	colon
SW-620	colon
A549/ATCC	non-small cell lung
EKVX	non-small cell lung
HOP-62	non-small cell lung
HOP-92	non-small cell lung
NCI-H322M	non-small cell lung
NCI-H226	non-small cell lung
NCI-H23	non-small cell lung
NCI-H460	non-small cell lung
NCI-H522	non-small cell lung
LOX IMVI	melanoma
M14	melanoma
MALME-3M	melanoma
SK-MEL-2	melanoma
SK-MEL-28	melanoma
SK-MEL-5	melanoma
UACC-257	melanoma
UACC-62	melanoma
IGROV-1	ovarian
OVCAR-3	ovarian
OVCAR-4	ovarian
OVCAR-5	ovarian
OVCAR-8	ovarian
SK-OV-3	ovarian
DU-145	prostate
PC-3	prostate
786-O	renal
A498	renal
ACHN	renal
CAKI-1	renal

As shown in Figure 2, Siglec-15 was found to be expressed in several cancer types, in particular ovarian cancer, renal cancer, cancer of the central nervous system, and prostate cancer. In fact, Siglec-15 was detected in almost every cancer indication represented by these samples with the exception of leukemia. This result suggests that antibodies against Siglec-15 might have uses in cancer diseases.

The antibodies described in Example 2 (see below) may also be used for detection of Siglec-15 in cell lysates by immunoblotting. The entire open reading frame of human Siglec-15 cDNA was cloned into a mammalian expression vector

downstream of a CMV promoter (pCDNA-Siglec-15). This construct, or a control empty vector which does not encode Siglec-15, were transfected into A375 melanoma cells, which express low endogenous levels of Siglec-15 protein. A pool of stable transfectants was isolated by selection with G418. Cell lysates from Siglec-15-transfected (+) and control (-) A375 cells were analysed by immunoblotting with monoclonal antibody E6. As shown in Figure 13A, the antibody detects a single band of 35 kDa in the Siglec-15-transfected cells, but not in control cells. This closely matches the predicted molecular weight of Siglec-15 (35.62 kDa), based on the primary amino acid sequence (http://www.bioinformatics.org/sms/prot_mw.html). Lysates were also analyzed by immunoblotting with an anti-β-actin antibody to demonstrate that similar total amounts of lysates were loaded in each lane. This result demonstrates that, by immunoblotting, antibody E6 recognizes, in a highly specific manner, overexpressed Siglec-15 in lysates from cells transfected with cloned Siglec-15 cDNA.

To confirm that the increased Siglec-15 mRNA levels in differentiated human PBMNC (Figure 1) correspond to an increase in Siglec-15 protein levels, lysates were prepared from human PBMNC treated with MCSF alone (non-differentiated, C) or MCSF and RANKL (differentiated, Δ) (Figure 13B). Lysates were also prepared from RAW 264.7 cells left untreated (non-differentiated, C) or treated with RANKL (differentiated, Δ) (Figure 13C). RAW 264.7 cells were shown previously to upregulate Siglec-15 mRNA levels upon induction of osteoclast differentiation by RANKL (Sooknanan, 2007). Analysis of these lysates by immunoblotting with antibody E9 demonstrates that, as predicted by RT-PCR studies, there is a dramatic increase in Siglec-15 protein levels both in PBMNC and RAW 264.7 cells upon differentiation into osteoclasts (Figure 13B and 13C).

RT-PCR analysis of mRNA from the NCI60 panel (Figure 2) indicated that a particularly high proportion of CNS-derived cancer cell lines express Siglec-15, while a recent microarray study found a small set of cancer cell lines, including the U87 glioblastoma line that is not part of the NCI60 panel, that express very high levels of Siglec-15 mRNA (Shankavaram, 2007). Therefore, we tested whether endogenous expression of Siglec-15 protein could be detected in U87 cells. Indeed, a protein the size of Siglec-15 is detected by immunoblotting of U87 cell lysates. To confirm the identity of this protein, U87 cells were transfected with a pool of small interfering RNAs (siRNAs) targeting Siglec-15 (SIGLEC15 siGENOME SMARTpool,

Dharmacon) (+) or with a control, non-targeting siRNA pool (-, Figure 13D) and allowed to grow for 72 h before cell lysis. Consistent with its identification as Siglec-15, treatment with the targeted siRNA resulted in reduced expression of this protein compared to the non-targeted control (Figure 13D). To examine whether Siglec-15 is found at the cell surface in cancer cells, we analyzed the siRNA-treated U87 cells by flow cytometry. Living cells were placed on ice and stained with Siglec-15 antibody E9 (see Example 2) or an isotype control antibody, under conditions which allow antibody binding to extracellular but not intracellular antigens. Treatment with the targeted siRNA resulted in reduced binding of antibody E9 but had no effect on binding of the control antibody (Figure 13E). Together, these results demonstrate that Siglec-15 may be expressed in cancer cells, and that it is accessible for antibody binding at the cell surface.

Example 2

This example provides details pertaining to the family of monoclonal antibodies that bind to Siglec-15.

To generate monoclonal antibodies, recombinant human Siglec-15 was produced in 293E cells using the large-scale transient transfection technology (Durocher et al., 2002; Durocher, 2004). A cDNA encoding amino acids 20 – 259 of SEQ ID NO:2 (see SEQ ID NO:123) was amplified by PCR using a forward primer that incorporated a BamHI restriction site (SEQ ID NO:124) and a reverse primer that incorporated a NotI restriction site (SEQ ID NO:125). The resulting PCR product was digested with BamHI and NotI and the fragment was ligated into the expression vector pYD5 (SEQ ID NO:126) that was similarly digested with the same restriction enzymes to create a vector called pYD5-0326. The pYD5 expression plasmid contains the coding sequence for the human Fc domain that allows fusion proteins to be generated as well as the sequence encoding the IgG1 signal peptide to allow the secretion of the fusion protein into the culture medium. For each milliliter of cells, one microgram of the expression vector, called pYD5-$0326_{20\text{-}259}$, was transfected in 2936E cells grown in suspension to a density of 1.5 – 2.0 million cells/ml. The transfection reagent used was polyethylenimine (PEI), (linear, MW 25,000, Cat# 23966 Polysciences, Inc., Warrington, PA) which was included at a DNA:PEI ratio of 1:3. Growth of the cells was continued for 5 days after which the culture medium was harvested for purification of the recombinant Fc-$0326_{20\text{-}259}$ fusion protein. The protein

was purified using Protein-A agarose as instructed by the manufacturer (Sigma-Aldrich Canada Ltd., Oakville, ON). A representative polyacrylamide gel showing a sample of the purified Fc-$0326_{20\text{-}259}$ (indicated as Fc-Siglec-$15_{20\text{-}259}$) is shown in Figure 3.

The antibodies that bind Siglec-15 were generated using the Biosite phage display technology. A detailed description of the technology and the methods for generating these antibodies can be found in the U.S. Patent No. 6,057,098. Briefly, the technology utilizes stringent panning of phage libraries that display the antigen binding fragments (Fabs). After a several rounds of panning, a library, termed the Omniclonal, was obtained that was enriched for recombinant Fabs containing light and heavy chain variable regions that bound to Siglec-15 with very high affinity and specificity. From this library, more precisely designated Omniclonal AL0025Z1, 96 individual recombinant monoclonal Fabs were prepared from E. coli and tested for Siglec-15 binding.

To measure the relative binding of each individual monoclonal antibody, recombinant human Fc-Siglec-$15_{20\text{-}259}$ was produced in 293E cells using the large-scale transient transfection technology (Durocher et al., 2002; Durocher, 2004). The 96-well master plate of monoclonal preparations contained different concentrations of purified anti-Siglec-15 Fabs in each well. A second stock master plate was prepared by diluting the Fabs to a final concentration of 10 μg/ml from which all subsequent dilutions were performed for ELISA measurements. To carry out the binding of Fc-Siglec-15 to the monoclonal preparations, the Fc-Siglec-$15_{20\text{-}259}$ was biotinylated with NHS-biotin (Pierce, Rockford, IL) and 10 ng/well was coated in a streptavidin 96-well plate. One nanogram of each Fab monoclonal preparation was added to each well and incubated at room temperature for 30 minutes. Bound antibody was detected with HRP-conjugated mouse anti-kappa light chain antibody in the presence of TMB liquid substrate (Sigma-Aldrich Canada Ltd., Oakville, ON) and readings were conducted at 450 nm in microtiter plate reader. As shown in Figure 4A, a total of 53 (highlighted dark grey) monoclonal antibodies displayed significant binding in this assay (>0.2 arbitrary OD_{450} units). The antibodies were purposely diluted to 1 ng/well to accentuate the binding of those antibodies with the most affinity for Siglec-15. Since the antibodies were generated using a Fc fusion protein, the monoclonals were also tested in an ELISA using biotinylated Fc domain only. As shown in Figure 4B, 17 antibodies interacted with the Fc moiety of the Fc-

Siglec-15_{20-259} (highlighted light grey). The values presented in bold (see Figure 4) represent the exemplary antibodies 25A1, 25B4, 25B8, 25C1, 25D8, 25E5, 25E6, and 25E9. These data also revealed that the binding of the antibodies varied from well to well indicating that they exhibited different affinities for Siglec-15.

The applicant noted that the antibody or antigen binding fragment of the present invention may bind efficiently to the antigen, in fact it was found that 1 ng of antibody is capable of binding to less than 500 ng of SEQ ID NO.:2.

The specificity of these antibodies for Siglec-15 was assessed by testing their binding to two other members of the Siglec family, CD33 and Siglec-2. CD33 (GeneBank™ accession No. NM_001772.3) is the prototype of the CD33-related family of Siglecs: among human proteins, these Siglecs share the highest amino acid sequence similarity with Siglec-15 (around 29% sequence identity between their two respective N-terminal Ig-like domains). Siglec-2 (GeneBank™ accession No. NM_001771.3) is less similar (23% sequence identity), but like Siglec-15 and unlike most other Siglecs, it has a marked preference for binding α2-6-linked sialic acid conjugates (Angata 2007, Blixt 2003). Sequences comprising the V-set and N-terminal C2-set Ig-like domains of Siglec-2 and CD33 (corresponding to the region of Siglec-15 used as the antigen for antibody production) were cloned from a human PBMNC cDNA library into the pYD5 vector. Supernatants from 293-6E cells transfected with these constructs, as wells as from non-transfected 293-6E cells or those transfected with pYD5-Siglec-15 or pYD5 empty vector, were analyzed by immunoblotting with an anti-Fc antibody to evaluate expression levels (Figure 14A). Transfection of these constructs resulted in expression of Fc-tagged proteins of the expected size (Figure 14A). Aliquots of these supernatants were adsorbed onto PVDF by vacuum dot blotting (Bio-dot apparatus, Bio-Rad), and binding of representative Siglec-15 monoclonal antibodies was evaluated (Western blots were not used because many antibodies react only with the native, non-denatured form of Siglec-15). As controls, anti-Fc and anti-Siglec-15 omniclonal antibodies reacted with all four Fc-tagged proteins (Figure 14B). In contrast, monoclonal antibodies D8 and E9 show no detectable binding to Fc alone, Siglec-2 or CD33, indicating that they are highly specific for Siglec-15.

Example 3

This example discloses the methods used to convert the Fabs into full IgG2 chimeric monoclonal antibodies. A scheme of the methodology is presented in Figure 5.

In order to conduct *in vitro* and *in vivo* studies to validate the biological function of the antigen the light and heavy chain variable regions contained in the Fabs was transferred to full antibody scaffolds, to generate mouse-human chimeric IgG2s. The expression vectors for both the light and heavy immunoglobulin chains were constructed such that i) the original bacterial signal peptide sequences upstream of the Fab expression vectors were replaced by mammalian signal peptides and ii) the light and heavy chain constant regions in the mouse antibodies were replaced with human constant regions. The methods to accomplish this transfer utilized standard molecular biology techniques that are familiar to those skilled in the art. A brief overview of the methodology is described here (see Figure 5).

Light chain expression vector – an existing mammalian expression plasmid, called pTTVH8G (Durocher et al., 2002), designed to be used in a 293E transient transfection system was modified to accommodate the mouse light chain variable region. The resulting mouse-human chimeric light chain contained a mouse variable region followed by the human kappa constant domain. The cDNA sequence encoding the human kappa constant domain was amplified by PCR with primers OGS1773 and OGS1774 (SEQ ID NOS:127 and 128, respectively). The nucleotide sequence and the corresponding amino acid sequence for the human kappa constant region are shown in SEQ ID NOS:129 and 130, respectively. The resulting 321 base pair PCR product was ligated into pTTVH8G immediately downstream of the signal peptide sequence of human VEGF A (NM_003376). This cloning step also positioned unique restriction endonuclease sites that permitted the precise positioning of the cDNAs encoding the mouse light chain variable regions. The sequence of the final expression plasmid, called pTTVK1, is shown in SEQ ID NO:131. Based on the sequences disclosed in Table 2, PCR primers specific for the light chain variable regions of antibodies 25A1, 25B4, 25B8, 25C1, 25D8, 25E5, 25E6, and 25E9 (SEQ ID NOS:37, 41, 45, 49, 53, 57, 61, and 65, respectively) were designed that incorporated, at their 5'-end, a sequence identical to the last 20 base pairs of the VEGF A signal peptide. The sequences of these primers are shown in SEQ ID NO:132 for 25A1; SEQ ID NO:133 for 25B4, 25B8, 25C1, 25D8, and 25E9; SEQ ID NO:134 for 25E5, and SEQ ID NO:135 for 25E6, respectively. The same

reverse primer was used to amplify all four light chain variable regions since the extreme 3'-ends were identical. This primer (SEQ ID NO:136) incorporated, at its 3'-end, a sequence identical to the first 20 base pairs of the human kappa constant domain. Both the PCR fragments and the digested pTTVK1 were treated with the 3' – 5' exonuclease activity of T4 DNA polymerase resulting in complimentary ends that were joined by annealing. The annealing reactions were transformed into competent *E. coli* and the expression plasmids were verified by sequencing to ensure that the mouse light chain variable regions were properly inserted into the pTTVK1 expression vector. Those skilled in the art will readily recognize that the method used for construction of the light chain expression plasmids applies to all anti-Siglec-15 antibodies contained in the original Fab library.

Heavy chain expression vector – the expression vector that produced the heavy chain immunoglobulins was designed in a similar manner to the pTTVK1 described above for production of the light chain immunoglobulins. In the case of the chimeric anti-Siglec-15 antibodies, IgG2 isotype was required which is the preferred type for stable, blocking antibodies. To this end, the constant regions (CH1, CH2, and CH3) of the human IgG2 immunoglobulin were amplified and ligated into a pre-existing IgG1 expression vector and the detailed methods are described herein. Plasmid pYD11 (Durocher et al., 2002), which contains the human IgGK signal peptide sequence as well as the CH2 and CH3 regions of the human Fc domain of IgG1, was modified by ligating the cDNA sequence encoding the human constant CH1 region. PCR primers OGS1769 and OGS1770 (SEQ ID NOS:137 and 138), designed to contain unique restriction endonuclease sites, were used to amplify the human IgG1 CH1 region containing the nucleotide sequence and corresponding amino acid sequence shown in SEQ ID NOS:139 and 140. Following ligation of the 309 base pair fragment of human CH1 immediately downstream of the IgGK signal peptide sequence, the resulting plasmid was digested with the restriction enzymes ApaI and NsiI. These enzymes that digest both the constant IgG1 and IgG2 cDNAs in exactly the same positions that permits the IgG1 constant sequence to be replaced by the human IgG2 sequence in the expression vector. The cDNA encoding the human IgG2 constant domains was obtained from a commercially available source (Open Biosystems, Huntsville, AL). The final plasmid used to express the IgG2 immunoglobulin heavy chain was designated pYD19 and the sequence is shown in SEQ ID NO:141. When a selected heavy chain variable region is ligated

into this vector, the resulting plasmid encodes a full IgG2 heavy chain immunoglobulin with human constant regions. Based on the sequences disclosed in Table 2, PCR primers specific for the heavy chain variable regions of antibodies 25A1, 25B4, 25B8, 25C1, 25D8, 25E5, 25E6, and 25E9 (SEQ ID NOS:39, 43, 47, 51, 55, 59, 63, and 67, respectively) were designed that incorporated, at their 5'-end, a sequence identical to the last 20 base pairs of the IgGK signal peptide. The sequences of these primers are shown in SEQ ID NOS:142 for 25A1; SEQ ID NO:143 for 24B4 and 25D8; SEQ ID NO:144 for 25B8, 25C1, and 25E9; SEQ ID NO:145 for 25E5; and SEQ ID NO:146 for 25E6, respectively. The same reverse primer was used to amplify all four heavy chain variable regions since the extreme 3'-ends were identical. This primer (SEQ ID NO:147) incorporated, at its 3'-end, a sequence identical to the first 20 base pairs of the human CH1 constant domain. Both the PCR fragments and the digested pYD19 were treated with the 3' – 5' exonuclease activity of T4 DNA polymerase resulting in complimentary ends that were joined by annealing. The annealing reactions were transformed into competent *E. coli* and the expression plasmids were verified by sequencing to ensure that the mouse heavy chain variable regions were properly inserted into the pYD19 expression vector. Those skilled in the art will readily recognize that the method used for construction of the heavy chain expression plasmids applies to all anti-Siglec-15 antibodies contained in the original Fab library.

Expression of human IgG2s in 293E cells – The expression vectors prepared above that encoded the light and heavy chain immunoglobulins were expressed in 293E cells using the transient transfection system (Durocher et al., 2002). By virtue of the signal peptides incorporated at the amino-termini of both immunoglobulin chains, the mature IgG2 was harvested from the serum-free culture medium of the cells. The methods used for co-transfecting the light and heavy chain expression vectors were described herein. For each milliliter of cells, one microgram of a combination of both the light and heavy chain expression plasmids was transfected in 293E cells grown in suspension to a density of 1.5 – 2.0 million cells/ml. The ratio of light to heavy chain plasmid was optimized in order to achieve the most yield of antibody in the tissue culture medium and it was found to be 9:1 (L:H). The transfection reagent used was polyethylenimine (PEI), (linear, MW 25,000, Cat# 23966 Polysciences, Inc., Warrington, PA) which was included at a DNA:PEI ratio of 1:3. Growth of the cells was continued for 5 days after which the culture medium was

harvested for purification of the IgG2 chimeric monoclonal antibodies. The protein was purified using Protein-A agarose as instructed by the manufacturer (Sigma-Aldrich Canada Ltd., Oakville, ON).

To determine the relative binding affinity of selected monoclonals more accurately, increasing concentration of the Fabs was incubated with biotinylated Fc-Siglec-15_{20-259}. Ten nanograms of biotinylated Fc-Siglec-15_{20-259} was coated in streptavidin microtiter plates and increasing amounts of either Fabs or the chimeric IgG2 monclonals 25B4, 25B8, 25C1, 25D8, 25E6, and 25E9 were added as indicated in Figure 6. As depicted in Figure 6, the binding of the 25B4, 25B8, 25C1, 25D8, 25E6, and 25E9 chimeric IgG2 monoclonal antibodies was very similar to the Fabs. This result shows that the transposition of the variable domains from the mouse Fabs into a human IgG2 backbone did not significantly affect the capacity of the light and heavy chain variable regions to confer Siglec-15 binding.

Example 4

This example describes the use of anti-Siglec-15 antibodies for inhibiting the differentiation of osteoclasts.

Human PBMNCs (AllCells, Emoryville, CA) were placed in the appropriate culture medium for 24 h at 37 C in a 5% CO_2 atmosphere. The cells were seeded in 96-well plates at a cell density of 100,000 cells/ml and treated with increasing concentration (0.01 μg/ml – 100 μg/ml) of anti-Siglec-15 IgG2 chimeric monoclonal antibodies in the presence of 35 ng/ml M-CSF and 30 ng/ml RANKL. Undifferentiated precursor cells were treated only with M-CSF, The control wells were treated with a non-Siglec-15 binding IgG2. The cells were fixed, stained for TRAP, and multinucleated cells counted and photographed (magnification 40X). As depicted in Figure 7, mAbs targeting Siglec-15 could efficiently inhibit the differentiation of human osteoclasts in a dose-dependent manner. Inhibition of osteoclast differentiation was observed to varying extents with every exemplary Siglec-15 antibody that was tested but the most active monoclonals were 25B8, 25E6, and 25E9. Cells treated with a control chimeric IgG2 were not inhibited (see lower right panels in Figure 8, *Control IgG2*). This result is in complete agreement with the experiments disclosed by Sooknanan (Sooknanan et al., 2007) that showed that knockdown of Siglec-15 expression by RNA interference caused inhibition of human osteoclast differentiation.

The biological function of differentiated osteoclasts is to resorb bone and thus the activity of osteoclasts should also be inhibited by antibodies that target Siglec-15. To test this, human PBMNCs were seeded on synthetic calcium phosphate substrate discs (BD BioCoat™ Osteologic™ MultiTest Slides) and cultured in similar conditions as described above. The precursor cells were treated with M-CSF and RANKL in the presence of either a control isotype IgG or the 25D8 or 25E9 anti-Siglec-15 antibodies. The antibodies were at a concentration of 1 μg/ml or 10 μg/ml. Once fully matured osteoclasts were present in the control untreated wells. The cells were scarped off the discs and the remaining bone substrate was stained using a standard von Kossa stain which renders the calcium mineral brown. As shown in Figure 12, the wells containing undifferentiated osteoclasts (upper left panel, *M-CSF*) showed no evidence of degradation of the substrate which appears as white spots on the surface (degradation pits). As expected, the cells treated with RANKL had evidence of significant degradation and the surface contained many pits (lower left panel, *M-CSF + RANKL*). Similarly, the osteoclasts treated with the control IgG could also degrade the bone substrate which demonstrated that these control antibodies did not inhibit osteoclast activity non-specifically. When the differentiating osteoclasts were treated with the anti-Siglec-15 antibodies, the 25E9 candidate efficiently inhibited bone degradation in this assay (Figure 12, right panels). By contrast, the 25D8 antibody did not inhibit degradation in this assays (see middle-right panels of Figure 12). Taken together, these results (Figure 7 and Figure 12) demonstrate that antibodies against Siglec-15 inhibit osteoclast differentiation and bone degradation activity.

In a parallel experiment, mouse PBMNCs were treated in a similar manner. As depicted in Figure 8, anti-Siglec-15 chimeric antibodies could inhibit the differentiation of mouse osteoclasts as exemplified by the chimeric mAbs designated 25B8, 25E6, and 25D8. This result confirms that the monoclonal antibodies that were generated against the human orthologue of Siglec-15 are cross-reactive against the mouse Siglec-15 protein as well. This was experimentally verified using an ELISA. A fragment of the mouse Siglec-15 cDNA was amplified corresponding to amino acids 21-256 using oligonucleotides containing the sequences shown in SEQ ID NOS: 159 and 160. This PCR fragment was ligated into the pYD5 expression vector as was described for the human Siglec-15 fragment for expression in 293-6E cells. The

recombinant Fc-mouseSiglec-15 was purified using Protein-A affinity chromatography.

An exemplary anti-Siglec-15 monoclonal Fab designated 25C8 was incubated with either Fc-human(h)Siglec-15_{20-259} or Fc-mouse(m)Siglec-15_{21-256}. The results (see Figure 9) indicate that the binding activity of the antibodies that were generated against the human Siglec-15 also cross-react with the mouse orthologue of Siglec-15.

The results described above clearly demonstrate the importance of Siglec-15 in osteoclastogenesis. Attenuation of Siglec-15 expression in osteoclast precursor cells results in cells that are highly impaired in their ability to form multinucleated mature osteoclasts. Thus, targeting Siglec-15 with an inhibitor, in particular a therapeutic monoclonal antibody, would prove to be a very selective way to target those cells that are directly responsible for bone degradation during acute metastatic bone cancer or chronic osteoporosis.

Example 5

This example pertains to the ability of anti-Siglec-15 antibodies to block binding of Siglec-15 to sialic acid (SA) conjugates.

The formation of sialylated glycoproteins is required for proper osteoclastogenesis (Takahata *et al.*, 2007). Siglec-15 binds sialic acid, and this binding is dependent on the amino acid residue R143 (Angata 2007). One mechanism by which Siglec-15 antibodies inhibit osteoclast formation could involve interference with their target's sialic acid-binding function due to interactions with an epitope encompassing R143. To examine this possibility, we performed an ELISA-based assay to test the ability of Siglec-15 antibodies to block binding of recombinant Fc-Siglec-15 to Neu5Aca2-6-GalNAc-PAA-Biotin (Glycotech, Rockville, MD), which is a preferred, sialic acid-containing binding partner of Siglec-15 (Angata 2007). Fc-Siglec-15 was immobilized on a Protein A-coated microtiter plate, and different Siglec-15 antibodies were then applied. After incubation and removal of unbound antibody, Neu5Aca2-6-GalNAc-PAA-Biotin was added. This biotinylated probe should form a complex with Siglec-15 only if an antibody is not blocking the sialic acid binding site. The presence of the biotinylated probe was detected using streptavidin-HRP by standard methods. As shown in Figure 15, anti-Siglec-15 omniclonal and 25D8 antibodies inhibit sialic acid binding compared to a non-

targeting, control antibody. Antibody E6 also has a clear, but less pronounced effect. Antibody E9 has little effect, indicating that its epitope does not overlap with the sialic acid binding site. Addition of a control antibody (Figure 15, see *ctl IgG2*) did not prevent the binding of sialic acid moiety to Siglec-15. The method was highly dependent on the presence of Siglec-15 since no binding was detected when only the Fc was coated in the plates nor was there any binding when the SA was omitted (Figure 15, see *no SA*, *Fc + SA*, and *Fc only*). Together, these results demonstrate that the Siglec-15 monoclonal antibodies can interfere, to varying extents, with the sialic acid binding function of Siglec-15 likely due to interactions near R143. This property could be important for their effects on osteoclastogenesis.

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SEQUENCE LISTINGS

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AGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG
AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG
CTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

SEQ ID NO:10

DIVMTQAAFSNPVTLGTSASISCRSSKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPYTFGGGTKLEIKVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
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SEQ ID NO:11

CAGGTCCAAGTGCAGCAGCCTGGGGCTGAAATTGTGAGGCCTGGGGCTTCAGTGAAGCTGTC
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AAGTTCAAGAGCAAGGCCACACTGACTGTAGACAAATCCTCCAGCACAGCCTACATGCAACT
CAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGGGGGGGACGGGGACT
ACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCAGCCTCAACGAAGGGCCCA
TCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCCGCCCTGGGCTG
CCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTGACCA
GCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG
GTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCC
CAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCC
CAGCACCACCTGTGGCAGGACCGTCAGTCTTCCGCTTCCCCCCAAAACCCAAGGACACCCGC
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GGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGG
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GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACACCTCC
CATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGT
GGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACG
CAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

SEQ ID NO:12

QVQVQQPGAEIVRPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGLINPTNGRTNYNE
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VTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTL
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SEQ ID NO:13
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AGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG
AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG
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SEQ ID NO:14
DIVMTQAAPSVPVTPGESVSISCRSTKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIKVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
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SEQ ID NO:15
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CAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTACTGTACAACTTTCTACTATAGTCACT
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CAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTAC
TCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAA
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AGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCGCTTCCCCCCAAAA
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AGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACA
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CAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCG
TGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

SEQ ID NO:16
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KFKGKATLTADRSSTTAYMELSSLTSEDSAVYYCTTFYYSHYNYDVGFAYWGQGTLVTVSAA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPK
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VHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
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SEQ ID NO:17
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GTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGAACTGCTTTCACACTGAGAATCAGTAGAGT
GGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAACATCTAGAATATCCTTTCACGTTCG
GAGGGGGGACCAAGCTGGAAATAAAACGGGCTGTGGCTGCACCATCTGTCTTCATCTTCCCG
CCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTA
TCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGG
AGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG
AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG
CTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

SEQ ID NO:18
DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIKVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:19
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CAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTACTGTACAAGTTTCTACTATACTTACT
ATAATTACGACGTGGGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCAGCC
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CATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGT
CCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
AAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCA
CAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG
CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGG

AGAACAACTACAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

SEQ ID NO:20
EIQLQQSGAELVRPGASVTLSCKASGYTFTDYEMHWVKQTPVHGLEWIGAIDPETGGTAYNQ
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STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTV
VHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
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SEQ ID NO:21
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GTCCCAGACAGGTTCAGTAGCAGTGGGTCAGGAACTGATTTCACACTGAGAATCAGCAGAGT
GGAGGCTGAGGATGTGGGTGTTTATTACTGTGCTCAAAATCTAGAACTTCCGTACACGTTCG
GAGGGGGGACCAAGCTGGAAATAAAACGGGCTGTGGCTGCACCATCTGTCTTCATCTTCCCG
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TCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGG
AGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG
AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG
CTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

SEQ ID NO:22
DIVMTQAAFSNPVTLGTSASISCRSSKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASG
VPDRFSSSGSGTDFTLRISRVEAEDVGVYYCAQNLELPYTFGGGTKLEIKVAAPSVFIFPPS
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ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:23
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CAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGGGGGGGACGGGGACT
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CATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGT
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CAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

SEQ ID NO:24
QVQVQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGLINPSNARTNYNE
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SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDW
LNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
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SEQ ID NO:25
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ACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAG
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SEQ ID NO:26
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KVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:27
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CGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCGCTTCCCCCCAAAACCCAAGGAC
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CGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC
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CCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCAC
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SEQ ID NO:28

EVKLEESGGGLVQPGGSLKLSCAASGFDFSKDWMSWVRQAPGKGLEWIGEINPDSSTINYAP
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GPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQ
DWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFY
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SEQ ID NO:29

AGTATTGTGATGACCCAGACTCCCAAATTCCTGCTTGTATCAGCAGGAGACAGGGTTACCAT
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ACTGGCAGTGGATATGGGACGGATTTCACTTTCACCATCACCACTGTGCAGGCTGAAGACCT
GGCAGTTTATTTCTGTCAGCAGGATTATACCTCTCCGTGGACGTTCGGTGGAGGCACCAAGC
TGGAAATCAAACGGGCTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAG
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AGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGC
AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTAC
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SEQ ID NO:30

SIVMTQTPKFLLVSAGDRVTITCKASQSVSNAVAWYQQKPGQSPKLLIYYTSNRYTGVPDRF
TGSGYGTDFTFTITTVQAEDLAVYFCQQDYTSPWTFGGGTKLEIKVAAPSVFIFPPSDEQLK
SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
HKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:31

CAGGTCCAACTGCAGCAGCCTGGGGCTGAACTGGCGAAGCCTGGGGCTTCAGTGAAGTTGTC
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CAGCGGCCTGACATCTGAGGACTCTGCGGTCTATTACTGTACAAGCCATACGTACTGGGGCC
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AGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGA
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SEQ ID NO:32

QVQLQQPGAELAKPGASVKLSCKASGYTFNTYNMYWLKQRPGQGLEWIGGIDPSNGDTKINE
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PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS
NFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEY
KCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK

SEQ ID NO:33

GATATTGTGATGACCCAGGCTGCACCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCAT
CTCCTGCAGGTCTACTAAGAGTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCC
TGCAGAGGCCAGGCCAGTCTCCTCAGCTCCTGATATATCGGATGTCCAACCTTGCCTCAGGA
GTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGAACTGCTTTCACACTGAGAATCAGTAGAGT
GGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAACATCTAGAATATCCTTTCACGTTCG
GAGGGGGGACCAAGCTGGAAATAAAACGGGCTGTGGCTGCACCATCTGTCTTCATCTTCCCG
CCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTA
TCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGG
AGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTG
AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG
CTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

SEQ ID NO:34

DIVMTQAAPSVPVTPGESVSISCRSTKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIKVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:35

GAGATCCAGCTGCAGCAGTCTGGAGTTGAGCTGGTGAGGCCTGGGGCTTCAGTGACGCTGTC
CTGCAAGGCTTCGGGCTACACATTTACTGACTATGACATGCACTGGGTGAAGCAGACACCTG
TTCATGGCCTGGAATGGATTGGAACTATTGATCCTGAAACTGGTGGTACTGCCTACAATCAG
AAGTTCAAGGGCAAGGCCACACTGACTGCGGACAGATCCTCCACCACAGCCTACATGGAGCT
CAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTACTGTACAAGTTTCTACTATACTTACT
CTAATTACGACGTGGGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCAGCC
TCAACTGGGGCGTCTTATTACTATGCTATGGACCACTGGGGTCAAGGAACCTCAGTCACCGT
CTCCTCAGCCTCAACGAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCT
CCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTC
AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCT

ACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAA
TGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCGCTT
CCCCCCAAAACCCAAGGACACCCGCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGG
TGGATGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTG
CATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGT
CCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
AAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCA
CAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTG
CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGG
AGAACAACTACAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

SEQ ID NO:36

EIQLQQSGVELVRPGASVTLSCKASGYTFTDYDMHWVKQTPVHGLEWIGTIDPETGGTAYNQ
KFKGKATLTADRSSTTAYMELSSLTSEDSAVYYCTSFYYTYSNYDVGFAYWGQGTLVTVSAA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY
SLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTV
VHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL
HNHYTQKSLSLSPGK

SEQ ID NO:37

GAAAATGTGCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCAGGGGAGAAGGTCACCAT
ATCCTGCAGTGCCAGCTCAAGTGTAAGTTACATGTACTGGTACCAGCAGAAGCCAGGATCCT
CCCCCAAACCCTGGATTTATCGCACATCCAACCTGGCTTCTGGAGTCCCTGCTCGCTTCAGT
GGCAGTGGGTCTGGGACCTCTTACTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGC
CACTTATTACTGCCAGCAGTGGAGTAGTAACCCACTCACGTTCGGTGCTGGGACCAAGCTGG
AGCTGAAA

SEQ ID NO:38

ENVLTQSPAIMSASPGEKVTISCSASSSVSYMYWYQQKPGSSPKPWIYRTSNLASGVPARFS
GSGSGTSYSLTISSMEAEDAATYYCQQWSSNPLTFGAGTKLELK

SEQ ID NO:39

GAGGTCCAGCTGCAACAATCTGGGACTGAGCTGGTGAGGCCTGGGTCCTCAGTGAAGATTTC
CTGCAAGGCTTCTGGCTACACCTTCACCAGGTACTGGATGGACTGGGTGAAGCAGAGGCCTG
GACAAGGCCTTGAGTGGATCGGAGAGATTGATCCTTCTGATAGTTATACTAACTACAATCAA
AAGTTCAAGGGCAAGGCCACATTGACTGTAGATAAATTCTCCAGAACAGCCTATATGGAACT
CAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGATCGGGGGCCTACTCTA
GTGACTATAGTTACGACGGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA

SEQ ID NO:40

EVQLQQSGTELVRPGSSVKISCKASGYTFTRYWMDWVKQRPGQGLEWIGEIDPSDSYTNYNQ
KFKGKATLTVDKFSRTAYMELSSLTSEDSAVYYCARSGAYSSDYSYDGFAYWGQGTLVTVSA

SEQ ID NO:41

GATATTGTGATGACCCAGGCTGCATTCTCCAATCCAGTCACTCTTGGAACATCAGCTTCCAT
CTCCTGCAGGTCTAGTAAGAGTCTCCTACATAGTAATGGCATCACTTATTTGTATTGGTATC
TGCAGAAGCCAGGCCAGTCTCCTCAGCTCCTGATTTATCAGATGTCCAACCTTGCCTCAGGA

GTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGAACTGCTTTCACACTGAGAATCAGTAGAGT
GGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAACATCTAGAATATCCGTACACGTTCG
GAGGGGGGACCAAGCTGGAAATAAAA

SEQ ID NO:42
DIVMTQAAFSNPVTLGTSASISCRSSKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPYTFGGGTKLEIK

SEQ ID NO:43
CAGGTCCAAGTGCAGCAGCCTGGGGCTGAAATTGTGAGGCCTGGGGCTTCAGTGAAGCTGTC
CTGCAAGGCTTCTGGCTACACCTTCACCAGCTACTGGATGCACTGGGTGAAGCAGAGGCCTG
GACAAGGCCTTGAGTGGATTGGACTGATTAATCCTACCAACGGTCGTACTAACTACAATGAG
AAGTTCAAGAGCAAGGCCACACTGACTGTAGACAAATCCTCCAGCACAGCCTACATGCAACT
CAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGGGGGGGACGGGGACT
ACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

SEQ ID NO:44
QVQVQQPGAEIVRPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGLINPTNGRTNYNE
KFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGGDGDYFDYWGQGTTLTVSS

SEQ ID NO:45
GATATTGTGATGACCCAGGCTGCACCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCAT
CTCCTGCAGGTCTACTAAGAGTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCC
TGCAGAGGCCAGGCCAGTCTCCTCAGCTCCTGATATATCGGATGTCCAACCTTGCCTCAGGA
GTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGAACTGCTTTCACACTGAGAATCAGTAGAGT
GGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAACATCTAGAATATCCTTTCACGTTCG
GAGGGGGGACCAAGCTGGAAATAAAA

SEQ ID NO:46
DIVMTQAAPSVPVTPGESVSISCRSTKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIK

SEQ ID NO:47
GAGATCCAGCTGCAGCAGTCTGGAGTTGAGCTGGTGAGGCCTGGGGCTTCAGTGACGCTGTC
CTGCAAGGCTTCGGGCTACACATTTACTGACTATGACATGCACTGGGTGAAGCAGACACCTG
TTCATGGCCTGGAATGGATTGGAACTATTGATCCTGAAACTGGTGGTACTGCCTACAATCAG
AAGTTCAAGGGCAAGGCCACACTGACTGCGGACAGATCCTCCACCACAGCCTACATGGAGCT
CAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTACTGTACAACTTTCTACTATAGTCACT
ATAATTACGACGTGGGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA

SEQ ID NO:48
EIQLQQSGVELVRPGASVTLSCKASGYTFTDYDMHWVKQTPVHGLEWIGTIDPETGGTAYNQ
KFKGKATLTADRSSTTAYMELSSLTSEDSAVYYCTTFYYSHYNYDVGFAYWGQGTLVTVSA

SEQ ID NO:49
GATATTGTGATGACCCAGGCTGCACCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCAT
CTCCTGCAGGTCTAGTAAGAGTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCC
TGCAGAGGCCAGGCCAGTCCCCTCAGCTCCTGATATATCGGATGTCCAACCTTGCCTCAGGA
GTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGAACTGCTTTCACACTGAGAATCAGTAGAGT
GGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAACATCTAGAATATCCTTTCACGTTCG
GAGGGGGGACCAAGCTGGAAATAAAA

SEQ ID NO:50
DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIK

SEQ ID NO:51
GAGATCCAGCTGCAGCAGTCTGGAGCTGAGCTGGTGAGGCCTGGGGCTTCAGTGACGCTGTC
CTGCAAGGCTTCGGGCTACACATTTACTGACTATGAAATGCACTGGGTGAAGCAGACACCTG
TTCATGGCCTGGAATGGATTGGAGCTATTGATCCTGAAACTGGTGGTACTGCCTACAATCAG
AAGTTCAAGGGCAAGGCCACACTGACTGCAGACAAATCCTCCAGCACAGCCTACATGGAGCT
CAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTACTGTACAAGTTTCTACTATACTTACT
ATAATTACGACGTGGGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA

SEQ ID NO:52
EIQLQQSGAELVRPGASVTLSCKASGYTFTDYEMHWVKQTPVHGLEWIGAIDPETGGTAYNQ
KFKGKATLTADKSSSTAYMELSSLTSEDSAVYYCTSFYYTYYNYDVGFAYWGQGTLVTVSA

SEQ ID NO:53
GATATTGTGATGACCCAGGCTGCATTCTCCAATCCAGTCACTCTTGGAACATCAGCTTCCAT
CTCCTGCAGGTCTAGTAAGAGTCTCCTACATAGTAATGGCATCACTTATTTGTATTGGTATC
TGCAGAAGCCAGGCCAGTCTCCTCAGCTCCTGATTTATCAGATGTCCAACCTTGCCTCAGGA
GTCCCAGACAGGTTCAGTAGCAGTGGGTCAGGAACTGATTTCACACTGAGAATCAGCAGAGT
GGAGGCTGAGGATGTGGGTGTTTATTACTGTGCTCAAAATCTAGAACTTCCGTACACGTTCG
GAGGGGGGACCAAGCTGGAAATAAAA

SEQ ID NO:54
DIVMTQAAFSNPVTLGTSASISCRSSKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASG
VPDRFSSSGSGTDFTLRISRVEAEDVGVYYCAQNLELPYTFGGGTKLEIK

SEQ ID NO:55
CAGGTCCAAGTGCAGCAGCCTGGGGCTGAGCTTGTGAAGCCTGGGGCTTCGGTGAAGCTGTC
CTGCAAGGCTTCTGGCTACACCTTCACCAGCTACTGGATGCACTGGGTGAAGCAGAGGCCTG
GACAAGGCCTTGAGTGGATTGGACTGATTAATCCTAGCAACGCTCGTACTAACTACAATGAG
AAGTTCAATACCAAGGCCACACTGACTGTAGACAAATCCTCCAGCACAGCCTACATGCAACT
CAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTACTGTGCAAGAGGGGGGGACGGGGACT
ACTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

SEQ ID NO:56
QVQVQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGLINPSNARTNYNE
KFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGGDGDYFDYWGQGTTLTVSS

SEQ ID NO:57
CAAATTGTTCTCACCCAGTCTCCAACACTCATGTCTGCATCTCCAGGGGAGAAGGTCACCAT
GACCTGCAGTGCCAGCTCAAGTGTAAGTTACATGTACTGGTACCAGCAGAAGCCAAGATCCT
CCCCCAAACCCTGGATTTATCGCACATCCAACCTGGTTTCTGGAGTCCCTGTACGCTTCAGT
GGCAGTGGGTCTGGGACCTCTTACTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGC
CACTTATTACTGCCAGCAGTGGAGTAGTAACCCACCCACGTTCGGTGCTGGGACCAAGCTGG
AGCTGAAA

SEQ ID NO:58

QIVLTQSPTLMSASPGEKVTMTCSASSSVSYMYWYQQKPRSSPKPWIYRTSNLVSGVPVRFS
GSGSGTSYSLTISSMEAEDAATYYCQQWSSNPPTFGAGTKLELK

SEQ ID NO:59
GAAGTGAAGCTTGAGGAGTCTGGAGGTGGCCTGGTGCAGCCTGGAGGATCCCTGAAACTCTC
CTGTGCAGCCTCAGGATTCGATTTTAGTAAAGACTGGATGAGTTGGGTCCGGCAGGCTCCAG
GGAAAGGGCTAGAATGGATTGGAGAAATTAATCCAGATAGCAGTACGATAAACTATGCACCA
TCTCTTAAGGATAAATTCATCATCTCCAGAGAGAACGCCAAAAATACGCTGTACCTGCAAAT
GAGCAAAGTGAGATCTGAGGACACAGCCCTTTATTACTGTTCAAGACTAGAGGACTACGAAG
ACTGGTACTTCGATGTCTGGGGCGCAGGGACCACGGTCACCGTCTCCTCA

SEQ ID NO:60
EVKLEESGGGLVQPGGSLKLSCAASGFDFSKDWMSWVRQAPGKGLEWIGEINPDSSTINYAP
SLKDKFIISRENAKNTLYLQMSKVRSEDTALYYCSRLEDYEDWYFDVWGAGTTVTVSS

SEQ ID NO:61
AGTATTGTGATGACCCAGACTCCCAAATTCCTGCTTGTATCAGCAGGAGACAGGGTTACCAT
AACCTGCAAGGCCAGTCAGAGTGTGAGTAATGCTGTAGCTTGGTACCAACAGAAGCCAGGGC
AGTCTCCTAAACTGCTGATATACTATACATCCAATCGCTACACTGGAGTCCCTGATCGCTTC
ACTGGCAGTGGATATGGGACGGATTTCACTTTCACCATCACCACTGTGCAGGCTGAAGACCT
GGCAGTTTATTTCTGTCAGCAGGATTATACCTCTCCGTGGACGTTCGGTGGAGGCACCAAGC
TGGAAATCAAA

SEQ ID NO:62
SIVMTQTPKFLLVSAGDRVTITCKASQSVSNAVAWYQQKPGQSPKLLIYYTSNRYTGVPDRF
TGSGYGTDFTFTITTVQAEDLAVYFCQQDYTSPWTFGGGTKLEIK

SEQ ID NO:63
CAGGTCCAACTGCAGCAGCCTGGGGCTGAACTGGCGAAGCCTGGGGCTTCAGTGAAGTTGTC
CTGCAAGGCTTCTGGCTACACCTTCAACACCTATAATATGTACTGGTTGAAACAGAGGCCTG
GGCAAGGCCTTGAGTGGATTGGGGGGATTGATCCTAGCAATGGTGATACTAAAATCAATGAG
AAGTTCAAGAACAAGGCCACACTGACTGTTGACAAATCCTCCAGTACAGCCTATATGCAACT
CAGCGGCCTGACATCTGAGGACTCTGCGGTCTATTACTGTACAAGCCATACGTACTGGGGCC
AAGGGACTCTGGTCACTGTCTCTGCA

SEQ ID NO:64
QVQLQQPGAELAKPGASVKLSCKASGYTFNTYNMYWLKQRPGQGLEWIGGIDPSNGDTKINE
KFKNKATLTVDKSSSTAYMQLSGLTSEDSAVYYCTSHTYWGQGTLVTVSA

SEQ ID NO:65
GATATTGTGATGACCCAGGCTGCACCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCAT
CTCCTGCAGGTCTACTAAGAGTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCC
TGCAGAGGCCAGGCCAGTCTCCTCAGCTCCTGATATATCGGATGTCCAACCTTGCCTCAGGA
GTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGAACTGCTTTCACACTGAGAATCAGTAGAGT
GGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAACATCTAGAATATCCTTTCACGTTCG
GAGGGGGGACCAAGCTGGAAATAAAA

SEQ ID NO:66
DIVMTQAAPSVPVTPGESVSISCRSTKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIK

SEQ ID NO:67
GAGATCCAGCTGCAGCAGTCTGGAGTTGAGCTGGTGAGGCCTGGGGCTTCAGTGACGCTGTC
CTGCAAGGCTTCGGGCTACACATTTACTGACTATGACATGCACTGGGTGAAGCAGACACCTG
TTCATGGCCTGGAATGGATTGGAACTATTGATCCTGAAACTGGTGGTACTGCCTACAATCAG
AAGTTCAAGGGCAAGGCCACACTGACTGCGGACAGATCCTCCACCACAGCCTACATGGAGCT
CAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTACTGTACAAGTTTCTACTATACTTACT
CTAATTACGACGTGGGGTTTGCTTACTGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA

SEQ ID NO:68
EIQLQQSGVELVRPGASVTLSCKASGYTFTDYDMHWVKQTPVHGLEWIGTIDPETGGTAYNQ
KFKGKATLTADRSSTTAYMELSSLTSEDSAVYYCTSFYYTYSNYDVGFAYWGQGTLVTVSA

SEQ ID NO:69
SASSSVSYMY

SEQ ID NO:70
RTSNLAS

SEQ ID NO:71
QQWSSNPLT

SEQ ID NO:72
GYTFTRYWMD

SEQ ID NO:73
EIDPSDSYTN

SEQ ID NO:74
ARSGAYSSDYSYDGFAY

SEQ ID NO:75
RSSKSLLHSNGITYLY

SEQ ID NO:76
QMSNLAS

SEQ ID NO:77
MQHLEYPYT

SEQ ID NO:78
GYTFTSYWMH

SEQ ID NO:79
LINPTNGRTN

SEQ ID NO:80
ARGGDGDYFDY

SEQ ID NO:81
RSTKSLLHSNGNTYLY

SEQ ID NO:82
RMSNLAS

SEQ ID NO:83
MQHLEYPFT

SEQ ID NO:84
GYTFTDYDMH

SEQ ID NO:85
TIDPETGGTA

SEQ ID NO:86
TTFYYSHYNYDVGFAY

SEQ ID NO:87
RSSKSLLHSNGNTYLY

SEQ ID NO:88
RMSNLAS

SEQ ID NO:89
MQHLEYPFT

SEQ ID NO:90
GYTFTDYEMH

SEQ ID NO:91
AIDPETGGTA

SEQ ID NO:92
TSFYYTYYNYDVGFAY

SEQ ID NO:93
RSSKSLLHSNGITYLY

SEQ ID NO:94
QMSNLAS

SEQ ID NO:95
AQNLELPYT

SEQ ID NO:96
GYTFTSYWMH

SEQ ID NO:97
LINPSNARTN

SEQ ID NO:98
ARGGDGDYFDY

SEQ ID NO:99
SASSSVSYMY

SEQ ID NO:100
RTSNLVS

SEQ ID NO:101
QQWSSNPPT

SEQ ID NO:102
GFDFSKDWMS

SEQ ID NO:103
EINPDSSTIN

SEQ ID NO:104
SRLEDYEDWYFDV

SEQ ID NO:105
KASQSVSNAVA

SEQ ID NO:106
YTSNRYT

SEQ ID NO:107
QQDYTSPWT

SEQ ID NO:108
GYTFNTYNMY

SEQ ID NO:109
GIDPSNGDTK

SEQ ID NO:110
TSHTY

SEQ ID NO:111
RSTKSLLHSNGNTYLY

SEQ ID NO:112
RMSNLAS

SEQ ID NO:113
MQHLEYPFT

SEQ ID NO:114
GYTFTDYDMH

SEQ ID NO:115
TIDPETGGTA

SEQ ID NO:116
TSFYYTYSNYDVGFAY

SEQ ID NO:117
GTAAGCAAGCTTGCTCACGCCTTCCGCGCGCTC

SEQ ID NO:118
GTAAGCAGATCTCTGGCGCCATGGAAGCGGAACAG

SEQ ID NO:119
CACTGGGAGCTATGGAAGAAGAC

SEQ ID NO:120
CAAAAGTGCAAAGAAGGGAAGACA

SEQ ID NO:121
TGAAGGTCGGAGTCAACGGATTTGGT

SEQ ID NO:122
CATGTGGGCCATGAGGTCCACCAC

SEQ ID NO:123
VRTKIDTTENLLNTEVHSSPAQRWSMQVPPEVSAEAGDAAVLPCTFTHPHRHYDGPLTAIWR
AGEPYAGPQVFRCAAARGSELCQTALSLHGRFRLLGNPRRNDLSLRVERLALADDRRYFCRV
EFAGDVHDRYESRHGVRLHVTAAPRIVNISVLPSPAHAFRALCTAEGEPPPALAWSGPALGN
SLAAVRSPREGHGHLVTAELPALTHDGRYTCTAANSLGRSEASVYLFRFHGASGAS

SEQ ID NO:124
GTAAGCGGATCCGTGAGAACTAAAATAGATACTA

SEQ ID NO:125:
GTAAGCGCGGCCGCGCTGGCGCCATGGAAGCGGAACAGGTA

SEQ ID NO:126
GTACATTTATATTGGCTCATGTCCAATATGACCGCCATGTTGACATTGATTATTGACTAGTTA
TTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATA
ACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAAT
GACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGAGTATTT
ACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTCCGCCCCCTATTGA
CGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTACGGGACTTTCC
TACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAGTA
CACCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGT
CAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAATAACCCCGC
CCCGTTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCGTTT
AGTGAACCGTCAGATCCTCACTCTCTTCCGCATCGCTGTCTGCGAGGGCCAGCTGTTGGGCTC
GCGGTTGAGGACAAACTCTTCGCGGTCTTTCCAGTACTCTTGGATCGGAAACCCGTCGGCCTC
CGAACGGTACTCCGCCACCGAGGGACCTGAGCCAGTCCGCATCGACCGGATCGGAAAACCTCT
CGAGAAAGGCGTCTAACCAGTCACAGTCGCAAGGTAGGCTGAGCACCGTGGCGGGCGGCAGCG
GGTGGCGGTCGGGGTTGTTTCTGGCGGAGGTGCTGCTGATGATGTAATTAAAGTAGGCGGTCT
TGAGCCGGCGGATGGTCGAGGTGAGGTGTGGCAGGCTTGAGATCCAGCTGTTGGGGTGAGTAC
TCCCTCTCAAAAGCGGGCATGACTTCTGCGCTAAGATTGTCAGTTTCCAAAAACGAGGAGGAT

TTGATATTCACCTGGCCCGATCTGGCCATACACTTGAGTGACAATGACATCCACTTTGCCTTT
CTCTCCACAGGTGTCCACTCCCAGGTCCAAGTTTGCCGCCACCATGGAGACAGACACACTCCT
GCTATGGGTACTGCTGCTCTGGGTTCCAGGTTCCACTGGCGCCGGATCAACTCACACATGCCC
ACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAA
GGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA
AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA
GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCA
GGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCAT
CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCC
ATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCC
CAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCC
TCCCGTGTTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAG
GTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACAC
GCAGAAGAGCCTCTCCCTGTCTCCCGGGAAAGCTAGCGGAGCCGGAAGCACAACCGAAAACCT
GTATTTTCAGGGCGGATCCGAATTCAAGCTTGATATCTGATCCCCCGACCTCGACCTCTGGCT
AATAAAGGAAATTTATTTTCATTGCAATAGTGTGTTGGAATTTTTTGTGTCTCTCACTCGGAA
GGACATATGGGAGGGCAAATCATTTGGTCGAGATCCCTCGGAGATCTCTAGCTAGAGCCCCGC
CGCCGGACGAACTAAACCTGACTACGGCATCTCTGCCCCTTCTTCGCGGGGCAGTGCATGTAA
TCCCTTCAGTTGGTTGGTACAACTTGCCAACTGAACCCTAAACGGGTAGCATATGCTTCCCGG
GTAGTAGTATATACTATCCAGACTAACCCTAATTCAATAGCATATGTTACCCAACGGGAAGCA
TATGCTATCGAATTAGGGTTAGTAAAAGGGTCCTAAGGAACAGCGATGTAGGTGGGCGGGCCA
AGATAGGGGCGCGATTGCTGCGATCTGGAGGACAAATTACACACACTTGCGCCTGAGCGCCAA
GCACAGGGTTGTTGGTCCTCATATTCACGAGGTCGCTGAGAGCACGGTGGGCTAATGTTGCCA
TGGGTAGCATATACTACCCAAATATCTGGATAGCATATGCTATCCTAATCTATATCTGGGTAG
CATAGGCTATCCTAATCTATATCTGGGTAGCATATGCTATCCTAATCTATATCTGGGTAGTAT
ATGCTATCCTAATTTATATCTGGGTAGCATAGGCTATCCTAATCTATATCTGGGTAGCATATG
CTATCCTAATCTATATCTGGGTAGTATATGCTATCCTAATCTGTATCCGGGTAGCATATGCTA
TCCTAATAGAGATTAGGGTAGTATATGCTATCCTAATTTATATCTGGGTAGCATATACTACCC
AAATATCTGGATAGCATATGCTATCCTAATCTATATCTGGGTAGCATATGCTATCCTAATCTA
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SEQ ID NO:127
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SEQ ID NO:128
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SEQ ID NO:129
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SEQ ID NO:130
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SEQ ID NO:131
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SEQ ID NO:132
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SEQ ID NO:135
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SEQ ID NO:137
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SEQ ID NO:138
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SEQ ID NO:139
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SEQ ID NO:140
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SEQ ID NO:141
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SEQ ID NO:145
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SEQ ID NO:146
GGGTTCCAGGTTCCACTGGCCAGGTCCAACTGCAGCAGCCTGG

SEQ ID NO:147
GGGGCCAGGGGAAAGACAGATGGGCCCTTCGTTGAGGC

SEQ ID NO.:148
$RSX_{1a}X_{2a}SLLHSNGX_{3a}TYLY$
X_{1a} is a neutral hydrophilic amino acid
X_{3a} is an hydrophobic amino acid or asparagine.
X_{2a} is lysine or glutamic acid

SEQ ID NO.:149
$X_{1b}MSNLAS$
wherein X_{1b} is a basic amino acid.
SEQ ID NO.:150
$RX_{1c}SNLX_{2c}S$
wherein X_{1c} is methionine or threonine
wherein X_{2c} is an hydrophobic amino acid.

SEQ ID NO.:151
$X_{1d}QX_{2d}LEX_{3d}PX_{4d}T$
wherein X_{1d} is an hydrophobic amino acid;
wherein X_{2d} is a basic amino acid;
wherein X_{3d} is tyrosine or leucine, and;
wherein X_{4d} is an aromatic amino acid.

SEQ ID NO.:152
$QQWSSNPX_{1e}T$
Wherein X_{1e} is proline or leucine.

SEQ ID NO.:153
$GYTFX_{1f}X_{2f}YX_{3f}MX$
wherein X_{1f} is threonine or asparagine;
wherein X_{2f} is threonine, arginine, serine or aspartic acid;
wherein X_{3f} is tryptophan, asparagine, aspartic acid or glutamic acid, and;
wherein X_{4f} is tyrosine, histidine or aspartic acid.

SEQ ID NO.:154
GYTFTDYX$_{5f}$MH
Wherein X$_{5f}$ is an acidic amino acid.

SEQ ID NO.:155
LINPX$_{1g}$NX$_{2g}$RX$_{3g}$N
Wherein X$_{1g}$ is a neutral hydrophilic amino acid;
Wherein X$_{2g}$ is alanine or glycine, and;
Wherein X$_{3g}$ is proline ot threonine.

SEQ ID NO.:156
X$_{1h}$IDPETGGTA
Wherein X$_{1h}$ is alanine or threonine.

SEQ ID NO.:157
EIX$_{1i}$PX$_{2i}$X$_{3i}$SX$_{4i}$X$_{5i}$N
Wherein X$_{1i}$ is aspartic acid or asparagine;
Wherein X$_{2i}$ is aspartic acid or serine;
Wherein X$_{3i}$ is aspartic acid or serine;
Wherein X$_{4i}$ is tyrosine or threonine, and;
Wherein X$_{5i}$ is threonine or isoleucine.

SEQ ID NO.:158
TX$_{1j}$FYYX$_{2j}$X$_{3j}$X$_{4j}$NYDVGFAY
Wherein X$_{1j}$ is a neutral hydrophilic amino acid;
Wherein X$_{2j}$ is a neutral hydrophilic amino acid;
Wherein X$_{3j}$ is tyrosine or histidine, and;
Wherein X$_{4j}$ is tyrosine or serine.

SEQ ID NO.:159
GTAAGCGAATTCATGGTGAAAACTAGAAGAGACGC

SEQ ID NO.:160
GTAAGCAAGCTTTTAGCCGTGGAAGCGGAACAGG

SEQ ID NO.:161 (25B02 variable light chain DNA)
AACATCCAGATGACCCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAAACTGTC
ACCATCACATGTCGAGCAAGTGAGAATATTTACAGTTATTTAGCATGGTATCAACAG
AAGCAGGGAAAATCTCCTCAGCTCCTGGTCTATAATGCAAAAACCTTACCAGAAGGT
GTGTCAGTAAGGTTCAGTGGCAGTGGATCAGGCACACAGTTTTCTCTGAAGATCAAC
AACCTGCAGCCTGAAGATTTTGGGAGTTATCACTGTCAACATCATTATGGTGTTCCT
CTTACGTTCGGTTCTGGGACCAAGCTGGAGTTGAAA

SEQ ID NO.:162 (25B02 variable light chain amino acids)
NIQMTQSPASLSASVGETVTITC**RASENIYSYLA**WYQQKQGKSPQLLVY**NAKTLPE**G
VSVRFSGSGSGTQFSLKINNLQPEDFGSYHC**QHHYGVPLT**FGSGTKLELK

SEQ ID NO.:163 (25B02 variable heavy chain DNA)
CAGGTGAAGCTTCAGCAGTCCGGGGCTGAGCTGGCAAGACCTGGGGCTTCAGTGAAG
TTTTCCTGCAAGGCTTCTGGCTACACCTTCACTAGGAACTGGATACAGTGGGTAAAA
CAGAGGCCTGGACAGGGTCTGGAATGGATTGGGGCTATTTATCCTGGAAATGGTGAT
AGTAGGTATACTCAGAAGTTCAAGGGCAAGGCCACATTGACTGCAGATAAATCCTCG
AACACAGCCTACATGCAACTCAGCGGTTTGGCATCTGAGGACTCTGCGGTCTATTAC
TGTGCAAGATTGGCTGGTAACTACGCTTACTACTTTGACTACTGGGGCCAAGGCACC
GCTCTCACAGTCTCCTCA

SEQ ID NO.:164 (25B02 variable heavy chain amino acids)
QVKLQQSGAELARPGASVKFSCKAS**GYTFTRNWIQ**WVKQRPGQGLEWIG**AIYPGNGD**
SRYTQKFKGKATLTADKSSNTAYMQLSGLASEDSAVYYC**ARLAGNYAYYFDY**WGQGT
ALTVSS

SEQ ID NO.:165 (25D11 variable light chain DNA)
GACATCCAGATGACCCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAAACTGTC
ACCATCACATGTCGAGCAAGTGGGAATATTCACAATTATTTAGCATGGTATCAACAG
AAGCAGGGAAAATCTCCTCAGCTCCTGGTCTATAATGCAAAAACCTTACCAGAAGGT
GTGTCAGTAAGGTTCAGTGGCAGTGGATCAGGCACACAGTTTTCTCTGAAGATCAAC
AACCTGCAGCCTGAAGATTTTGGGAGTTATCACTGTCAACATCATTATGGTGTTCCT
CTTACGTTCGGTTCTGGGACCAAGCTGGAGTTGAAA

SEQ ID NO.:166 (25D11 variable light chain amino acids)
DIQMTQSPASLSASVGETVTITC**RASGNIHNYLA**WYQQKQGKSPQLLVY**NAKTLPE**G
VSVRFSGSGSGTQFSLKINNLQPEDFGSYHC**QHHYGVPLT**FGSGTKLELK

SEQ ID NO.:167 (25D11 variable heavy chain DNA)
CAGGTGAAGCTTCAGCAGTCCGGGGCTGAGCTGGCAAGACCTGGGGCTTCAGTGAAG
TTTTCCTGCAAGGCTTCTGGCTACACCTTCACTAGGAACTGGATACAGTGGGTAAAA
CAGAGGCCTGGACAGGGTCTGGAATGGATTGGGGCTATTTATCCTGGAAATGGTGAT
AGTAGGTATACTCAGAAGTTCAAGGGCAAGGCCACATTGACTGCAGATAAATCCTCG
AACACAGCCTACATGCAACTCAGCGGTTTGGCATCTGAGGACTCTGCGGTCTATTAC
TGTGCAAGATTGGCTGGTAACTACGCTTACTACTTTGACTACTGGGGCCAAGGCACC
GCTCTCACAGTCTCCTCA

SEQ ID NO.:168 (25D11 variable heavy chain amino acids)
QVKLQQSGAELARPGASVKFSCKAS**GYTFTRNWIQ**WVKQRPGQGLEWIG**AIYPGNGD**
SRYTQKFKGKATLTADKSSNTAYMQLSGLASEDSAVYYC**ARLAGNYAYYFDY**WGQGT
ALTVSS

SEQ ID NO.:169 (25E10 variable light chain DNA)
GACATCCAGATGACCCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAAACTGTC
ACCATCACATGTCGAGCAAGTGGGAATATTCACAATTATTTAGCATGGTATCAGCAG
AAACAGGGAAAATCTCCTCAGCTCCTGGTCTATAATGCAAAAACCCTAGCAGATGGT
GTGCCATCAAGGTTCAGTGGCAGTGGATCAGGAACACAATATTCTCTCAAGATCAAC
AGCCTGCAGCCTGAAGATTTTGGGAGTTATTACTGTCAACATCATTACGGTGCTCCT
CTTACGTTCGGTGCTGGGACCAAGGTGGAGCTGAAA

SEQ ID NO.:170 (25E10 variable light chain amino acids)
DIQMTQSPASLSASVGETVTITC**RASGNIHNYLA**WYQQKQGKSPQLLVY**NAKTLAD**G
VPSRFSGSGSGTQYSLKINSLQPEDFGSYYC**QHHYGAPLT**FGAGTKVELK

SEQ ID NO.:171 (25E10 variable heavy chain DNA)
GATGTGCAGCTGCAACAATCTGGGGCTGAGCTGGCAAGACCTGGGGCTTCAGTGAAG
TTTTCCTGCAAGGCTTCTGGCTACACCTTTACTAGGAACTGGATACAGTGGGTTAAA
CAGAGGCCTGGACAGGGTCTGGAATGGATTGGGGCTGTTTATCCTGGAAATGGTGAT
AGTAGGTATACTCAGAAGTTCAAGGGCAAGGCCACATTGACTGCAGATAAATCCTCC
AGCACAGCCTACATGCAACTCAACAGTTTGTCATCTGAGGACTCTGCGGTCTATTAC
TGCGCAAGATTGGCTGGTAACTACGCTTACTACTTTGACTACTGGGGCCAAGGCACC
GCTCTCACAGTCTCCTCA

SEQ ID NO.:172 (25E10 variable heavy chain amino acids)
DVQLQQSGAELARPGASVKFSCKAS**GYTFTRNWIQ**WVKQRPGQGLEWIG**AVYPGNGD**
SRYTQKFKGKATLTADKSSSTAYMQLNSLSSEDSAVYYC**ARLAGNYAYYFDY**WGQGT
ALTVSS

SEQ ID NO.:173
RASENIYSYLA

SEQ ID NO.:174
NAKTLPE

SEQ ID NO.:175
QHHYGVPLT

SEQ ID NO.:176
GYTFTRNWIQ

SEQ ID NO.:177
AIYPGNGDSR

SEQ ID NO.:178
ARLAGNYAYYFDY

SEQ ID NO.:179
RASGNIHNYLA

SEQ ID NO.:180
NAKTLPE

SEQ ID NO.:181
QHHYGVPLT

SEQ ID NO.:182
GYTFTRNWIQ

SEQ ID NO.:183
AIYPGNGDSR

SEQ ID NO.:184
ARLAGNYAYYFDY

SEQ ID NO.:185
RASGNIHNYLA

SEQ ID NO.:186
NAKTLAD

SEQ ID NO.:187
QHHYGAPLT

SEQ ID NO.:188
GYTFTRNWIQ

SEQ ID NO.:189
AVYPGNGDSR

SEQ ID NO.:190
ARLAGNYAYYFDY

Table 5A: Anti-siglec-15 heavy chain variable sequences.

ID	FR1	CDR-H1	FR2	CDR-H2	FR3	CDR-H3	FR4
25E6	QVQLQQPGAELAKPGASVKLSCKAS	GYTFNTYNMY	WLKQRPGQGLEWIG	GIDPSNGDTK	INEKFKNKATLTVDKSSSTAYMQLSGLTSEDSAVYYC	TSH----------TY	WGQGTLVTVSA
25H10	QVQLQQPGAELAKPGASVKLSCKAS	GYTFNTYNMY	WLKQRPGQGLEWIG	GIDPSNGDTK	INEKFKNKATLTVDKSSSTAYMQLSGLTSEDSAVYYC	TSH----------TY	WGQGTLVTVSA
25H11	QVQLQQPGAELAKPGASVKLSCKAS	GYTFNTYNMY	WLKQRPGQGLEWIG	GIDPSNGDTK	INEKFKNKATLTVDKSSSTAYMQLSGLTSEDSAVYYC	TSH----------TY	WGQGTLVTVSA
25A3	QVQLQQSRAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKNKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25A5	QVQVQQPGAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPSNARTN	YNEKFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25A11	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25B4	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25B12	QVQLQQSRAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKNKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25C9	QVQVQQPGAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPSNARTN	YNEKFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25C10	QVQVQQPGAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPSNARTN	YNEKFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25D3	QVQLQQSRAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKNKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25D4	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25D5	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25D6	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25D8	QVQVQQPGAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPSNARTN	YNEKFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25D10	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25E7	QVQVQQPGTELVKPGASVKLSCKAS	GYTFTTYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25E8	QVQLQQSRAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKNKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25E12	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMHLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F2	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F3	QVQVQQPGAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPSNARTN	YNEKFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F5	QVQVQQPGTELVKPGASVKLSCKAS	GYTFTTYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F6	QVQVQQPGAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPSNARTN	YNEKFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F7	EIQLQQSGTELVKPGASVKLSCKAS	GYTFTTYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F9	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F10	QVQVQQPGTELVKPGASVKLSCKAS	GYTFTTYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F11	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25F12	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKNKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25G3	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQREGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25G4	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS

Table 5A: Anti-siglec-15 heavy chain variable sequences.

ID	FR1	CDR-H1	FR2	CDR-H2	FR3	CDR-H3	FR4
25G7	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25G8	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25H1	QVQVQQPGTELVKPGASVKLSCKAS	GYTFTTYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25H2	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25H5	QVQLQQSRAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKNKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25H6	QVQLQQSGAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPSNGRPN	YNERFKTKATLTVDKSSSTAYMHLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25H7	QVQVQQPGAELVKPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPSNARTN	YNEKFNTKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25H8	QVQVQQPGAEIVRPGASVKLSCKAS	GYTFTSYWMH	WVKQRPGQGLEWIG	LINPTNGRTN	YNEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYC	ARGGDGDYF------DY	WGQGTTLTVSS
25B2	QVKLQQSGAELARPGASVKFSCKAS	GYTFTRNWIQ	WVKQRPGQGLEWIG	AIYPGNGDSR	YTQKFKGKATLTADKSSNTAYMQLSGLASEDSAVYYC	ARLAGNYAYYF----DY	WGQGTALTVSS
25D11	QVKLQQSGAELARPGASVKFSCKAS	GYTFTRNWIQ	WVKQRPGQGLEWIG	AIYPGNGDSR	YTQKFKGKATLTADKSSNTAYMQLSGLASEDSAVYYC	ARLAGNYAYYF----DY	WGQGTALTVSS
25E10	DVQLQQSGAELARPGASVKFSCKAS	GYTFTRNWIQ	WVKQRPGQGLEWIG	AVYPGNGDSR	YTQKFKGKATLTADKSSSTAYMQLNSLSSEDSAVYYC	ARLAGNYAYYF----DY	WGQGTALTVSS
25E5	EVKLEESGGGLVQPGGSLKLSCAAS	GFDFSKDWMS	WVRQAPGKGLEWIG	EINPDSSTIN	YAPSLKDKFIISRENAKNTLYLQMSKVRSEDTALYYC	SRLEDYEDWYF----DV	WGAGTTVTVSS
25B6	QAYLQQSGVELVRPGASVTLSCKAS	GYTFTDYDMH	WVKQTPVHGLEWIG	TIDPETGGTA	YNQKFKGKATLTADRSSTTAYMELSSLTSEDSAVYYC	TSFYYTYSNYDVGF-AY	WGQGTLVTVSA
25B11	EIQLQQSGVELVRPGASVTLSCKAS	GYTFTDYDMH	WVKQTPVHGLEWIG	TIDPETGGTA	YNQKFKGKATLTADRSSTTAYMELSSLTSEDSAVYYC	TSFYYTYSNYDVGF-AY	WGQGTLVTVSA
25E9	EIQLQQSGVELVRPGASVTLSCKAS	GYTFTDYDMH	WVKQTPVHGLEWIG	TIDPETGGTA	YNQKFKGKATLTADRSSTTAYMELSSLTSEDSAVYYC	TSFYYTYSNYDVGF-AY	WGQGTLVTVSA
25C1	EIQLQQSGAELVRPGASVTLSCKAS	GYTFTDYEMH	WVKQTPVHGLEWIG	AIDPETGGTA	YNQKFKGKATLTADKSSSTAYMELSSLTSEDSAVYYC	TSFYYTYYNYDVGF-AY	WGQGTLVTVSA
25B8	EIQLQQSGVELVRPGASVTLSCKAS	GYTFTDYDMH	WVKQTPVHGLEWIG	TIDPETGGTA	YNQKFKGKATLTADRSSTTAYMELSSLTSEDSAVYYC	TTFYYSHYNYDVGF-AY	WGQGTLVTVSA
25A1	EVQLQQSGTELVRPGSSVKISCKAS	GYTFTRYWMD	WVKQRPGQGLEWIG	EIDPSDSYTN	YNQKFKGKATLTVDKFSRTAYMELSSLTSEDSAVYYC	ARSGAYSSDYSYDGFAY	WGQGTLVTVSA

Table 5B: Anti-siglec-15 light chain variable sequences.

ID	FR1	CDR-L1	FR2	CDR-L2	FR3	CDR-L3	FR4
25E6	SIVMTQTPKFLLVSAGDRVTITC	KASQSVS-----NAVA	WYQQKPGQSPKLLIY	YTSNRYT	GVPDRFTGSGYGTDFTFTITTVQAEDLAVYFC	QQDYTSPWT	FGGGTKLEIK
25H10	SIVMTQTPKFLLVSAGDRVTITC	KASQSVS-----NAVA	WYQQKPGQSPKLLIY	YTSNRYT	GVPDRFTGSGYGTDFTFTITTVQAEDLAVYFC	QQDYTSPWT	FGGGTKLEIK
25H11	SIVMTQTPKFLLVSAGDRVTITC	KASQSVS-----NAVA	WYQQKPGQSPKLLIY	YTSNRYT	GVPDRFTGSGYGTDFTFTITTVQAEDLAVYFC	QQDYTSPWT	FGGGTKLEIK
25A3	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25A5	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25A11	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25B4	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25B12	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25C9	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25C10	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25D3	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25D4	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25D5	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25D6	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25D8	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25D10	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25E7	DIVMTQAVFSNPVILGTPASISC	RSSKSLLHSNGVTYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25E8	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25E12	DIVMTQAAFSNPVTLGTSASISC	RSSESLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25F2	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25F3	DIVMTHAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25F5	DIVMTQAVFSNPVILGTPASISC	RSSKSLLHSNGVTYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25F6	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25F7	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25F9	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25F10	DIVMTQAVFSNPVILGTPASISC	RSSKSLLHSNGVTYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25F11	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25F12	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25G3	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25G4	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK

Table 5B: Anti-siglec-15 light chain variable sequences.

ID	FR1	CDR-L1	FR2	CDR-L2	FR3	CDR-L3	FR4
25G7	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25G8	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25H1	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25H2	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25H5	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25H6	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLEYPYT	FGSGTKLEIK
25H7	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	AQNLELPYT	FGGGTKLEIK
25H8	DIVMTQAAFSNPVTLGTSASISC	RSSKSLLHSNGITYLY	WYLQKPGQSPQLLIY	QMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPYT	FGGGTKLEIK
25B2	NIQMTQSPASLSASVGETVTITC	RASENIY-----SYLA	WYQQKQGKSPQLLVY	NAKTLPE	GVSVRFSGSGSGTQFSLKINNLQPEDFGSYHC	QHHYGVPLT	FGSGTKLELK
25D11	DIQMTQSPASLSASVGETVTITC	RASGNIH-----NYLA	WYQQKQGKSPQLLVY	NAKTLPE	GVSVRFSGSGSGTQFSLKINNLQPEDFGSYHC	QHHYGVPLT	FGSGTKLELK
25E10	DIQMTQSPASLSASVGETVTITC	RASGNIH-----NYLA	WYQQKQGKSPQLLVY	NAKTLAD	GVPSRFSGSGSGTQYSLKINSLQPEDFGSYYC	QHHYGAPLT	FGAGTKVELK
25E5	QIVLTQSPTLMSASPGEKVTMTC	SASSSV-----SYMY	WYQQKPRSSPKPWIY	RTSNLVS	GVPVRFSGSGSGTSYSLTISSMEAEDAATYYC	QQWSSNPPT	FGAGTKLELK
25B6	DIVMTQAAPSVPVTPGESVSISC	RSSKSLLHSNGNTYLY	WFLQRPGQSPQLLIY	RMSNLAS	GVPDRFSGSGSGTAFTLRLSRVEAEDVGVYYC	MQHLEYPFT	FGGGTKLEIK
25B11	DIVMTQAAPSVPVTPGESVSISC	RSTKSLLHSNGNTYLY	WFLQRPGQSPQLLIY	RMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPFT	FGGGTKLEIK
25E9	DIVMTQAAPSVPVTPGESVSISC	RSTKSLLHSNGNTYLY	WFLQRPGQSPQLLIY	RMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPFT	FGGGTKLEIK
25C1	DIVMTQAAPSVPVTPGESVSISC	RSSKSLLHSNGNTYLY	WFLQRPGQSPQLLIY	RMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPFT	FGGGTKLEIK
25B8	DIVMTQAAPSVPVTPGESVSISC	RSTKSLLHSNGNTYLY	WFLQRPGQSPQLLIY	RMSNLAS	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	MQHLEYPFT	FGGGTKLEIK
25A1	ENVLTQSPAIMSASPGEKVTISC	SASSSV-----SYMY	WYQQKPGSSPKPWIY	RTSNLAS	GVPARFSGSGSGTSYSLTISSMEAEDAATYYC	QQWSSNPLT	FGAGTKLELK

CLAIMS:

1. An isolated antibody or antigen binding fragment capable of binding to a polypeptide able to promote osteoclast differentiation and having a sequence at least 80% identical to amino acids 20 to 259 of Sialic-acid-binding immunoglobulin-like lectin 15 (Siglec-15; SEQ ID NO.:2), wherein said antibody or antigen binging fragment is capable of inhibiting osteoclast differentiation, bone resorption or is capable of blocking Siglec-15 from binding to a sialic acid.

2. The isolated antibody or antigen binding fragment of claim 1, wherein the antibody or antigen binding fragment is capable of inhibiting differentiation of osteoclast precursor cells into differentiated osteoclasts.

3. The isolated antibody or antigen binding fragment of claim 2, wherein the isolated antibody or antigen binding fragment is a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a human antibody or a fragment thereof.

4. The isolated antibody or antigen binding fragment of claim 3, characterized in that it is produced from an isolated mammalian cell.

5. The isolated antibody or antigen binding fragment of claim 4, wherein the isolated mammalian cell is a human cell.

6. The isolated antibody or antigen binding fragment of claim 5, wherein the isolated antibody is a monoclonal antibody, a chimeric antibody, a human antibody or a fragment thereof.

7. The isolated antibody or antigen binding fragment of claim 6, characterized in that it is a chimeric antibody or a human antibody comprising amino acids of a constant region of a human antibody or a fragment thereof.

8. The isolated antibody or antigen binding fragment of claim 7, wherein the constant region or fragment thereof is from an IgG1, IgG2, IgG3, or IgG4.

9. The isolated antibody or antigen binding fragment of claim 8, wherein the constant region is from an IgG2.

10. The isolated antibody or antigen binding fragment of claim 3, characterized in that it is a chimeric antibody or a human antibody comprising amino acids of a constant region of a human antibody or a fragment thereof.

11. The isolated antibody or antigen binding fragment of claim 10, wherein the constant region or fragment thereof is from an IgG1, IgG2, IgG3, or IgG4.

12. The isolated antibody or antigen binding fragment of claim 11, wherein the constant region is from an IgG2.

13. The isolated antibody or antigen binding fragment of claim 2, wherein the antigen binding fragment is a FV (scFv), a Fab, a Fab' or a $(Fab')_2$.

14. The isolated antibody or antigen binding fragment of claim 2, wherein the osteoclast precursor cell is a human osteoclast precursor cell.

15. The isolated antibody or antigen binding fragment of claim 8, wherein the human osteoclast precursor cell is a primary human osteoclast precursor cell.

16. The isolated antibody or antigen binding fragment of claim 9, , wherein the isolated antibody or antigen binding fragment is a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a human antibody or a fragment thereof.

17. The isolated antibody or antigen binding fragment of claim 16, , wherein the isolated antibody or antigen binding fragment is a monoclonal antibody, a chimeric antibody, a human antibody or a fragment thereof.

18. The isolated antibody or antigen binding fragment of claim 17, characterized in that it is a chimeric antibody or a human antibody comprising amino acids of a constant region of a human antibody or a fragment thereof.

19. The isolated antibody or antigen binding fragment of claim 18, wherein the constant region or fragment thereof is from an IgG1, IgG2, IgG3, or IgG4.

20. The isolated antibody or antigen binding fragment of claim 19, wherein the constant region is from an IgG2.

21. The antibody or antigen binding fragment of any one of claims 1 to 20, characterized in that binds to non-denatured Siglec-15.

22. The antibody or antigen binding fragment of claim 21, characterized in that it specifically binds to Siglec-15 and not Siglec-2 or CD33.

23. The antibody or antigen binding fragment of any one of claims 1 to 22, characterized in that 1ng of antibody is capable of binding to less than 500ng of SEQ ID NO.:2.

24. An isolated antibody or antigen binding fragment capable of specific binding to SEQ ID NO.:2 or to a variant having at least 80% sequence identity with amino acids 20 to 259 of SEQ ID NO.:2 and of detecting the SEQ ID NO.:2 or variant in ovarian cancer cells, renal cancer cells, cancer cells of the central nervous system, prostate cancer cells, melanoma cells, breast cancer cells, lung cancer cells or colon cancer cells.

25. An isolated antibody or antigen binding fragment capable of specific binding to SEQ ID NO.:2 or to a variant having at least 80% sequence identity with amino acids 20 to 259 of SEQ ID NO.:2 and of inhibiting the growth of ovarian cancer cells, renal cancer cells, cancer cells of the central nervous system, prostate cancer cells, melanoma cells, breast cancer cells, lung cancer cells or colon cancer cells.

26. The isolated antibody or antigen binding fragment of any one of claims 1 to 25, wherein said antibody comprise a light chain variable domain comprising a sequence selected from the group consisting of a sequence at least 70% identical to SEQ ID NO.:38, a sequence at least 70% identical to SEQ ID NO.:42, a sequence at least 70% identical to SEQ ID NO.:46, a sequence at least 70% identical to SEQ ID NO.:50, a sequence at least 70% identical to SEQ ID NO.:54, a sequence at least 70% identical to SEQ ID NO.:58, a sequence at least 70% identical to SEQ ID NO.:62, a sequence at least 70% identical to SEQ ID NO.:66, a sequence at least 70% identical to SEQ ID NO.:162, a sequence at least 70% identical to SEQ ID NO.:166 and a sequence at least 70% identical to SEQ ID NO.:170 .

27. The isolated antibody or antigen binding fragment of claim 1 or 26, wherein said antibody comprise a heavy chain variable domain comprising a sequence selected from the group consisting of a sequence at least 70% identical to SEQ ID NO.:40, a sequence at least 70% identical to SEQ ID NO.:44, a sequence at least 70% identical to SEQ ID NO.:48, a sequence at least 70% identical to SEQ ID NO.:52, a sequence at least 70% identical to SEQ ID NO.:56, a sequence at least 70% identical to SEQ ID NO.:60, a sequence at least 70% identical to SEQ

ID NO.:64, a sequence at least 70% identical to SEQ ID NO.:68, a sequence at least 70% identical to SEQ ID NO.:164, a sequence at least 70% identical to SEQ ID NO.:168 and a sequence at least 70% identical to SEQ ID NO.:172.

28. An isolated antibody or antigen binding fragment capable of specific binding to Siglec-15 or to a variant thereof, the antibody comprising:
    a) the 3CDRs of a light chain variable domain defined in SEQ ID NO:38 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:40,
    b) the 3CDRs of a light chain variable domain defined in SEQ ID NO:42 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:44;
    c) the 3CDRs of a light chain variable domain defined in SEQ ID NO:46 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:48;
    d) the 3CDRs of a light chain variable domain defined in SEQ ID NO:50 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:52;
    e) the 3CDRs of a light chain variable domain defined in SEQ ID NO:54 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:56;
    f) the 3CDRs of a light chain variable domain defined in SEQ ID NO:58 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:60;
    g) the 3CDRs of a light chain variable domain defined in SEQ ID NO:62 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:64,
    h) the 3CDRs of a light chain variable domain defined in SEQ ID NO:66 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:68,
    i) the 3CDRs of a light chain variable domain defined in SEQ ID NO:162 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:164,

j) the 3CDRs of a light chain variable domain defined in SEQ ID NO:166 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:168, and;

k) the 3CDRs of a light chain variable domain defined in SEQ ID NO:170 and the 3CDRs of a heavy chain variable domain defined in SEQ ID NO:172.

29. An isolated antibody or antigen binding fragment capable of specific binding to Siglec-15 or to a variant thereof, the antibody comprising:

a) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:194 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:191;

b) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:195 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:192;

c) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:196 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:193;

d) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:38 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:40;

e) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:42 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:44;

f) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:46 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:48;

g) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:50 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:52;

h) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:54 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:56;

i) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:58 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:60;

j) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:62 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:64,

k) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:66 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:68,

l) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:162 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:164,

m) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:166 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:168, and;

n) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:170 and a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:172.

30. The isolated antibody or antigen binding fragment of claim 29, characterized in that it comprises;

a) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:194 and having a CDRL1 as defined in SEQ ID NO.:148 or SEQ ID NO.:201, a CDRL2 as defined in SEQ ID NO.:149 and a CDRL3 as defined in SEQ ID NO.: 151 or SEQ ID NO.:203 and;

b) a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:191 and having a CDRH1 as defined in SEQ ID NO.:153 or SEQ ID NO.:205, a CDRH2 as defined in SEQ ID NO.:155 or SEQ ID NO.:207 and a CDRH3 having sequence ARGGDGDYFDY.

31. The isolated antibody or antigen binding fragment of claim 30, wherein the CDRL1 is selected from the group consisting of RSSKSLLHSNGITYLY, RSSKSLLHSNGVTYLY or RSSESLLHSNGITYLY.

32. The isolated antibody or antigen binding fragment of claims 29 or 30, wherein the CDRL2 is QMSNLAS.

33. The isolated antibody or antigen binding fragment of any one of claims 29 to 32 wherein the CDRL3 is selected from the group consisting of AQNLELPYT, MQHLEYPYT or AQNLEYPYT.
34. The isolated antibody or antigen binding fragment of any one of claims 29 to 33 wherein the CDRH1 is selected from the group consisting of GYTFTSYWMH and GYTFTTYWMH.
35. The isolated antibody or antigen binding fragment of any one of claims 29 to 34 wherein the CDRH2 is selected from the group consisting of LINPTNGRTN, LINPSNARTN and LINPSNGRPN.
36. The isolated antibody or antigen binding fragment of claim 29, characterized in that it comprises;
    a) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:195 and having a CDRL1 as defined in SEQ ID NO.:197, a CDRL2 as defined in SEQ ID NO.:198 and a CDRL3 as defined in SEQ ID NO.:204 and;
    b) a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:192 and having a CDRH1 having sequence GYTFTRNWIQ, a CDRH2 as defined in SEQ ID NO.:200 and a CDRH3 having sequence ARLAGNYAYYFDY.
37. The isolated antibody or antigen binding fragment of claim 36, wherein the CDRL1 is selected from the group consisting of RASGNIHNYLA and RASENIYSYLA.
38. The isolated antibody or antigen binding fragment of claims 36 or 37, wherein the CDRL2 is selected from the group consisting of NAKTLPE and NAKTLAD.
39. The isolated antibody or antigen binding fragment of any one of claims 36 to 38, wherein the CDRL3 is selected from the group consisting of QHHYGVPLT and QHHYGAPLT.
40. The isolated antibody or antigen binding fragment of any one of claims 36 to 39, wherein the CDRH2 is selected from the group consisting of AIYPGNGDSR and AVYPGNGDSR.
41. The isolated antibody or antigen binding fragment of claim 29, characterized in that it comprises;
    a) a light chain variable domain having at least 70% sequence identity with SEQ ID NO.:196 and having a CDRL1 as defined in SEQ ID NO.:202, a

CDRL2 as defined in SEQ ID NO.:150 and a CDRL3 as defined in SEQ ID NO.:151 or SEQ ID NO.:203, and;

b) a heavy chain variable domain having at least 70% sequence identity with SEQ ID NO.:193 and a CDRH1 as defined in SEQ ID NO.:154 or SEQ ID NO.:208, a CDRH2 as defined in SEQ ID NO.:156 or SEQ ID NO.:209 and a CDRH3 as defined in SEQ ID NO.:158 or SEQ ID NO.:210.

42. The isolated antibody or antigen binding fragment of claim 41, wherein the CDRL1 is selected from the group consisting of RSSKSLLHSNGNTYLY and RSTKSLLHSNGNTYLY.

43. The isolated antibody or antigen binding fragment of claims 41 or 42, wherein the CDRL2 is RMSNLAS.

44. The isolated antibody or antigen binding fragment of any one of claims 41 to 43, wherein the CDRL3 is MQHLEYPFT.

45. The isolated antibody or antigen binding fragment of any one of claims 41 to 44, wherein the CDRH1 is selected from the group consisting of GYTFTDYDMH and GYTFTDYEMH.

46. The isolated antibody or antigen binding fragment of any one of claims 41 to 45, wherein the CDRH2 is selected from the group consisting of TIDPETGGTA and AIDPETGGTA.

47. The isolated antibody or antigen binding fragment of any one of claims 41 to 46, wherein the CDRH3 is selected from the group consisting of TSFYYTYSNYDVGFAY, TSFYYTYYNYDVGFAY and TTFYYSHYNYDVGFAY.

48. An isolated antibody or antigen binding fragment capable of competing with the antibody or antigen binding fragment of any one of claims 1 to 47.

49. The isolated antibody or antigen binding fragment of any one of claims 1 to 48, wherein said antibody comprises a constant region or a fragment thereof.

50. The isolated antibody or antigen binding fragment of any one of claims 1 to 48, that is a scFv, a Fab, a Fab' or a $(Fab')_2$.

51. The isolated antibody or antigen binding fragment of any one of claims 1 to 49, wherein said antibody is a monoclonal antibody.

52. The isolated antibody or antigen binding fragment of any one of claims 1 to 49, wherein said antibody is a polyclonal antibody.

53. The isolated antibody of any one of claims 1 to 52, wherein said antibody is conjugated with a detectable moiety or a cytotoxic moiety.

54. A nucleic acid encoding a light chain variable domain and/or a heavy chain variable domain of the antibody or antigen binding fragment of any one of claims 26 to 47.

55. A vector comprising the nucleic acid of claim 54.

56. The vector of claim 55, wherein said vector is an expression vector.

57. An isolated cell comprising the nucleic acid of claim 54.

58. The isolated cell of claim 57, wherein said cell comprises a nucleic acid encoding a light chain variable domain and a nucleic acid encoding a heavy chain variable domain.

59. The isolated cell of claim 58, wherein said cell is capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

60. An isolated cell comprising or expressing the antibody or antigen binding fragment of any one of claims 1 to 53.

61. The isolated cell of claim 60, wherein said cell comprises a nucleic acid encoding a light chain variable domain and a nucleic acid encoding a heavy chain variable domain.

62. The isolated cell of claim 61, wherein said cell is capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

63. A pharmaceutical composition comprising at least one of the antibody or antigen binding fragment of any one of claims 1 to 53 and a pharmaceutically acceptable carrier.

64. A composition comprising at least one of the antibody or antigen binding fragment of any one of claims 1 to 53 and a carrier.

65. Use of at least one of the antibody or antigen binding fragment of any one of claims 1 to 53, in the treatment of bone loss.

66. Use of at least one of the antibody or antigen binding fragment of any one of claims 1 to 53, in the treatment of ovarian cancer, renal cancer, cancer of the central nervous system, prostate cancer, melanoma, breast cancer, lung cancer or colon cancer.

67. Use of at least one of the antibody or antigen binding fragment of any one of claims 1 to 53, in the diagnosis of bone loss or bone disease.

68. Use of at least one of the antibody or antigen binding fragment of any one of claims 1 to 53, in the diagnosis of ovarian cancer, renal cancer, cancer of the central nervous system, prostate cancer, melanoma, breast cancer, lung cancer or colon cancer.

69. A method of treating bone loss, the method comprising administering at least one of the antibody or antigen binding fragment of any one of claims 1 to 53, to a mammal in need.

70. A method of treating ovarian cancer, renal cancer, cancer of the central nervous system, prostate cancer, melanoma, breast cancer, lung cancer or colon cancer, the method comprising administering at least one of the antibody or antigen binding fragment of any one of claims 1 to 53, to a mammal in need.

71. A method of detecting bone loss or bone diseases, the method comprising administering at least one of the antibody or antigen binding fragment of any one of claims 1 to 53, to a mammal in need.

72. A method of detecting ovarian cancer, renal cancer, cancer of the central nervous system, prostate cancer, melanoma, breast cancer, lung cancer or colon cancer, the method comprising administering at least one of the antibody or antigen binding fragment of any one of claims 1 to 53, to a mammal in need.

73. A method of detecting SEQ ID NO.:2 or a SEQ ID NO:2 variant having at least 80% sequence identity with amino acids 20 to 259 of SEQ ID NO:2, the method comprising contacting a cell expressing SEQ ID NO:2 or the SEQ ID NO:2 variant or a sample comprising or suspected of comprising SEQ ID NO:2 or the SEQ ID NO:2 variant with at least one of the antibody or antigen binding fragment of any one of claims 1 to 53 and measuring binding.

74. The method of claim 73, wherein the sample is from a mammal.

75. The method of claim 74, wherein the mammal suffers or is suspected of suffering from bone loss.

76. The method of claim 74, wherein the mammal has or is suspected of having ovarian cancer, renal cancer, cancer of the central nervous system, prostate cancer, melanoma, breast cancer, lung cancer or colon cancer.

77. The method of any one of claims 73 to 76, wherein the sample is a serum sample, a plasma sample or a blood sample obtained from the mammal.

78. The method of any one of claims 73 to 76, wherein the sample is a tissue sample obtained from the mammal.

79. The method of claim 73, wherein the sample is a cell culture supernatant.

80. The method of any one of claims 78 to 79, comprising quantifying the amount of antibody bound to SEQ ID NO:2 or to the SEQ ID NO:2 variant.

81. A kit comprising the antibody of any one of claims 1 to 53.

82. Use of SEQ ID NO:2 or a fragment of at least 10 amino acids thereof to generate antibodies for the diagnosis or treatment of bone loss, ovarian cancer, renal cancer, cancer of the central nervous system, prostate cancer, melanoma, breast cancer, lung cancer or colon cancer.

83. The use according to claim 82, wherein the fragment is comprised within amino acid 20 to 259 of SEQ ID NO:2.

84. A method of generating an antibody or antigen binding fragment capable of inhibiting differentiation of an osteoclast precursor cell (into a differentiated osteoclast) or of inhibiting a resorptive activity of an osteoclast, the method comprising administering SEQ ID NO.:2, a variant having at least 80% identity with SEQ ID NO.:2 or a fragment of at least 10 amino acids thereof, to a mammal.

85. The method of claim 84, further comprising isolating or purifying the antibody or antigen binding fragment.

86. The method according to claim 85, wherein the fragment is comprised within amino acids 20 to 259 of SEQ ID NO.:2.

87. A method of identifying a compound capable of inhibiting the growth of ovarian cancer cells, renal cancer cells, cancer cells of the central nervous system,

prostate cancer cells, melanoma cells, breast cancer cells, lung cancer cells or colon cancer cells, the method comprising providing a polypeptide comprising a region at least 80% identical to amino acids 20 to 259 of SEQ ID NO.:2 or a cell expressing said polypeptide with a candidate compound and measuring the activity or expression of the polypeptide, whereby a reduced activity or expression of the polypeptide positively identifies a suitable inhibitory compound.

88. The method of claim 87, wherein the candidate compound specifically binds to the polypeptide.

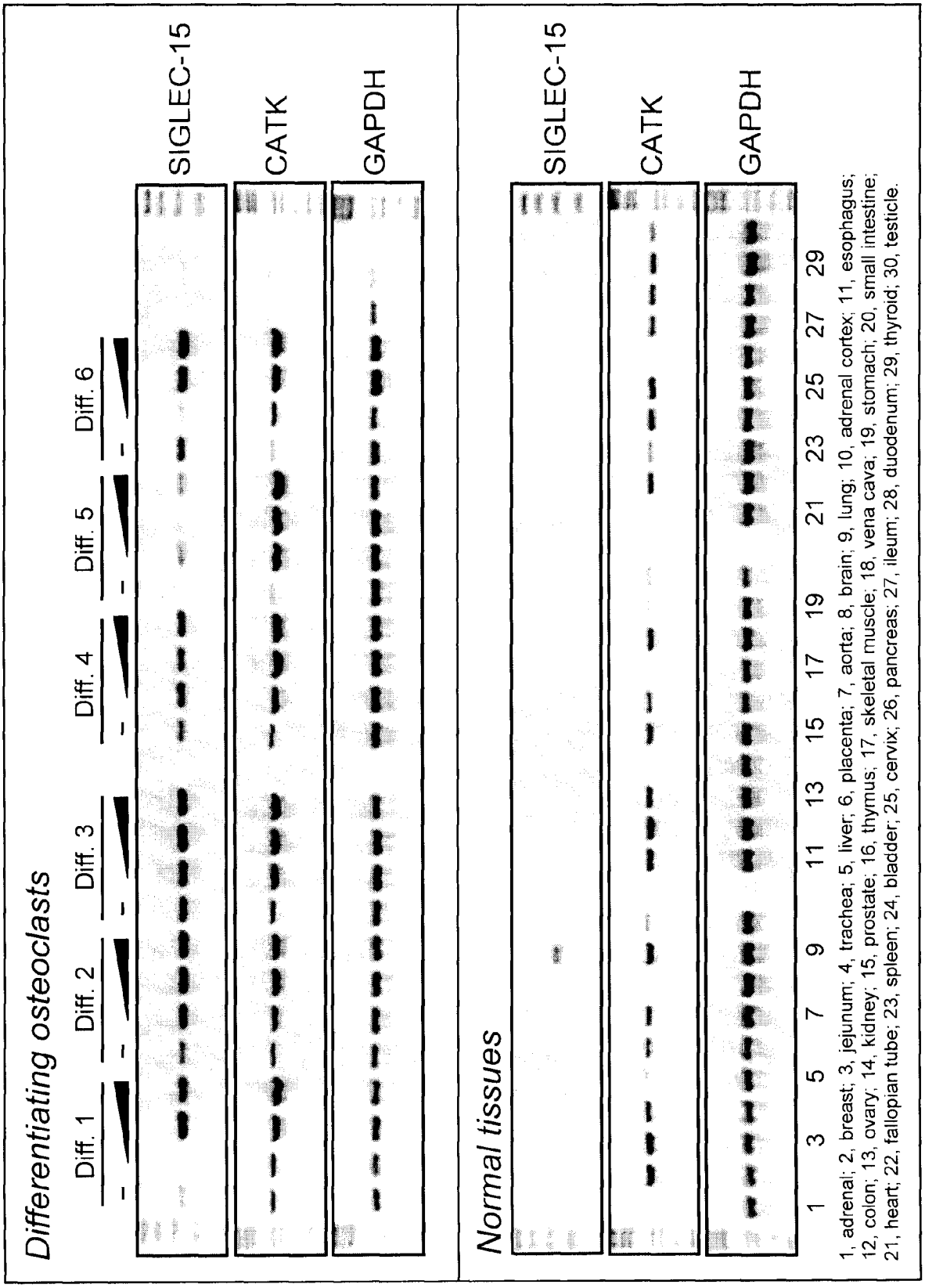
89. The method of claim 88, wherein the candidate compound is an antibody or an antigen binding fragment.

90. The method of claim 89, wherein the candidate compound is a siRNA or an antisense.

91. A method for inhibiting the growth of a cancer cell selected from the group consisting of ovarian cancer cells, renal cancer cells, cancer cells of the central nervous system, prostate cancer cells, melanoma cells, breast cancer cells, lung cancer cells or colon cancer cells, the method comprising providing the cancer cell with a nucleic acid capable of impairing the expression of a polypeptide at least 80% identical to SEQ ID NO.:2, wherein the cancer cell expresses the polypeptide at least 80% identical to SEQ ID NO.:2.

92. The method of claim 90, wherein the nucleic acid is a siRNA or an antisense.

FIGURE 1


Differentiating osteoclasts
Diff. 1
Diff. 2
Diff. 3
Diff. 4
Diff. 5
Diff. 6
SIGLEC-15
CATK
GAPDH
Normal tissues
SIGLEC-15
CATK
GAPDH
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29
1, adrenal; 2, breast; 3, jejunum; 4, trachea; 5, liver; 6, placenta; 7, aorta; 8, brain; 9, lung; 10, adrenal cortex; 11, esophagus; 12, colon; 13, ovary; 14, kidney; 15, prostate; 16, thymus; 17, skeletal muscle; 18, vena cava; 19, stomach; 20, small intestine; 21, heart; 22, fallopian tube; 23, spleen; 24, bladder; 25, cervix; 26, pancreas; 27, ileum; 28, duodenum; 29, thyroid; 30, testicle.

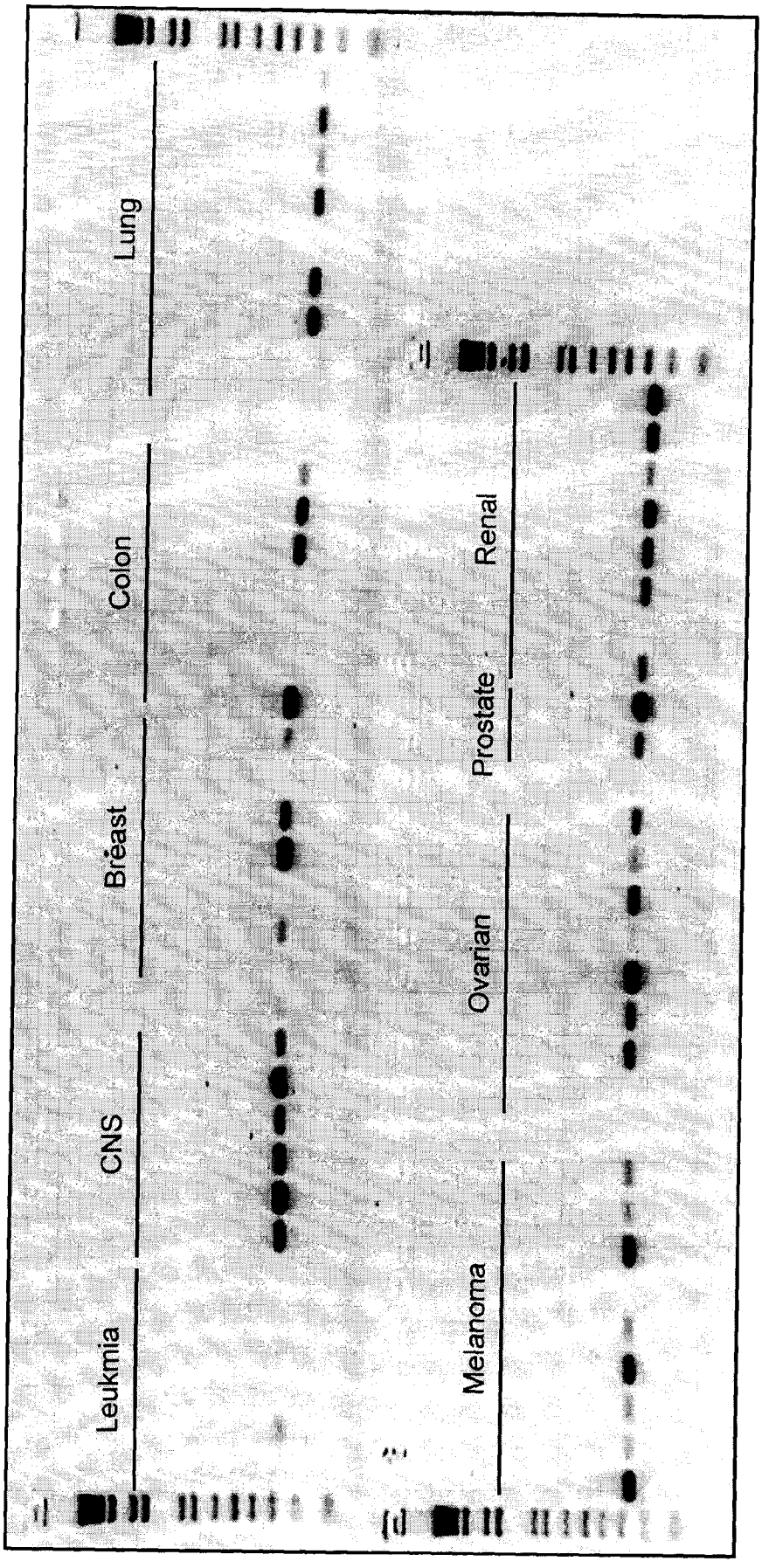

Leukmia
CNS
Breast
Colon
Lung
Melanoma
Ovarian
Prostate
Renal

FIGURE 2

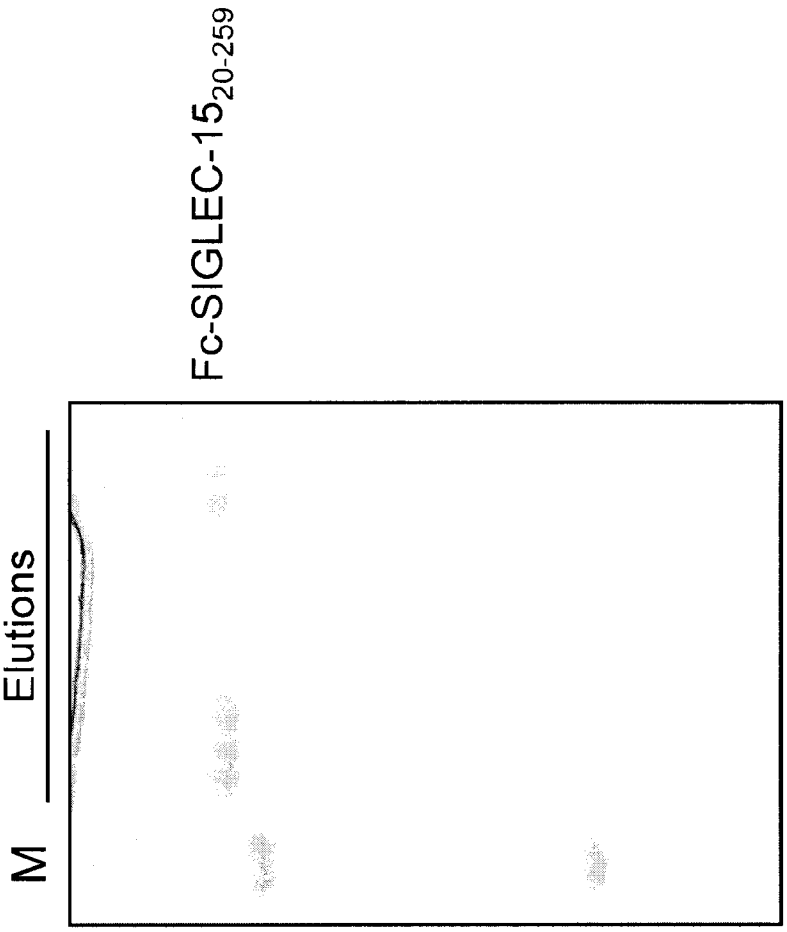


FIGURE 4

FIGURE 5

A

ELISA with biotinylated Fc-SIGLEC-15_{20-259}

	1	2	3	4	5	6	7	8	9	10	11	12
A	**0.793**	0.828	1.079	0.151	0.98	0.125	0.133	0.133	0.136	0.15	0.782	0.384
B	0.603	0.158	0.147	**1.001**	0.143	0.313	0.141	**0.613**	0.716	0.156	0.457	1.052
C	**0.473**	0.155	0.443	0.134	0.118	1.005	0.163	0.517	0.966	0.93	1.059	0.151
D	0.152	0.17	1.319	1.118	1.07	1.094	0.161	**0.909**	0.155	0.979	0.158	0.148
E	0.354	0.167	0.952	0.169	**0.312**	**0.436**	0.518	0.968	**0.491**	0.13	0.169	1.018
F	0.142	1.131	1.111	1.027	0.573	0.751	0.818	0.15	0.845	0.512	0.888	0.997
G	0.153	0.162	1.106	0.854	0.509	0.246	0.732	0.869	0.39	0.847	0.356	0.221
H	0.916	1.254	0.18	0.31	1.192	1.219	0.905	0.868	0.24	0.518	0.479	1.115

B

ELISA with biotinylated Fc

	1	2	3	4	5	6	7	8	9	10	11	12
A	**0.118**	1.879	0.112	0.119	0.119	0.113	0.102	1.002	0.123	0.101	0.133	1.603
B	1.811	0.129	0.123	**0.12**	0.124	0.134	0.231	**0.151**	1.872	0.185	0.124	0.152
C	**0.168**	0.185	1.585	0.13	0.161	0.122	0.138	1.771	0.167	0.16	1.946	0.261
D	0.117	0.173	0.134	0.12	0.133	0.128	0.133	**0.137**	0.152	0.209	0.219	0.255
E	1.284	0.126	1.883	0.138	**0.132**	**0.135**	0.135	0.12	**0.143**	0.151	0.139	0.148
F	0.116	0.146	0.14	1.805	0.197	0.145	0.144	0.132	0.158	0.152	0.13	0.14
G	0.128	0.13	0.138	0.128	0.137	0.134	0.126	0.125	0.135	0.134	0.132	0.146
H	0.128	0.139	0.13	0.124	0.141	0.147	0.136	0.138	0.131	0.127	0.134	1.982

FIGURE 5

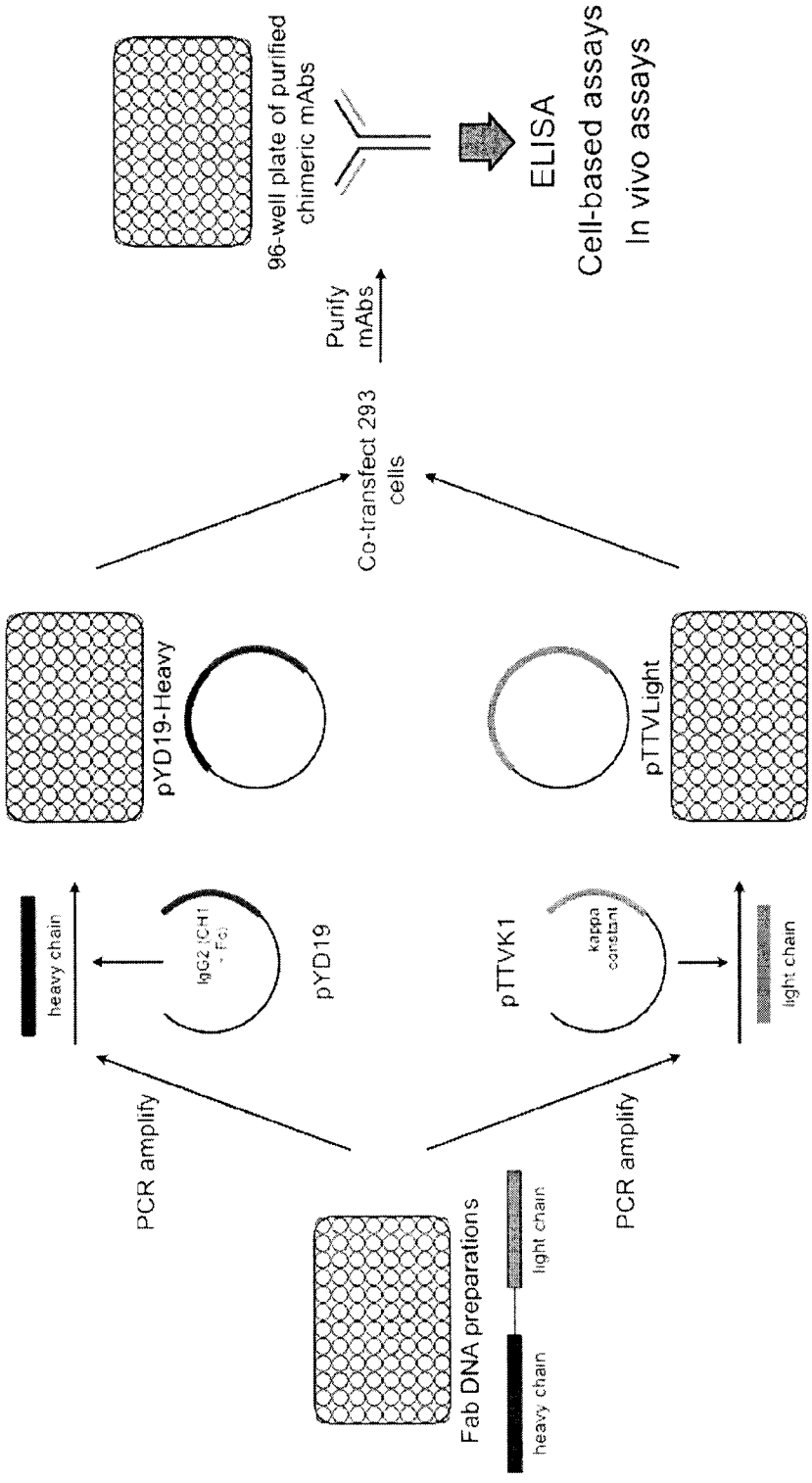
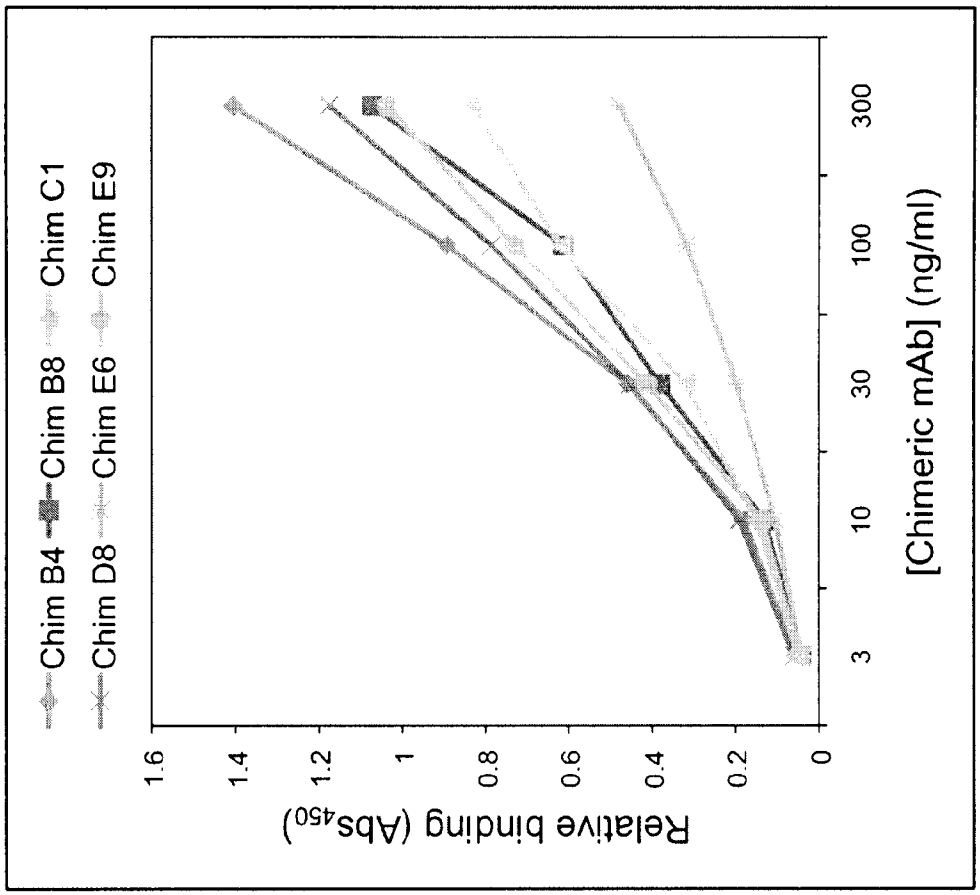

96-well plate of purified chimeric mAbs
ELISA
Cell-based assays
In vivo assays
Purify mAbs
Co-transfect 293 cells
pYD19-Heavy
pTTVLight
heavy chain
pYD19
pTTVK1
kappa constant
light chain
PCR amplify
PCR amplify
Fab DNA preparations
heavy chain
light chain

FIGURE 6


Chim B4
Chim B8
Chim C1
Chim D8
Chim E6
Chim E9
Relative binding (Abs450)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
3
10
30
100
300
[Chimeric mAb] (ng/ml)

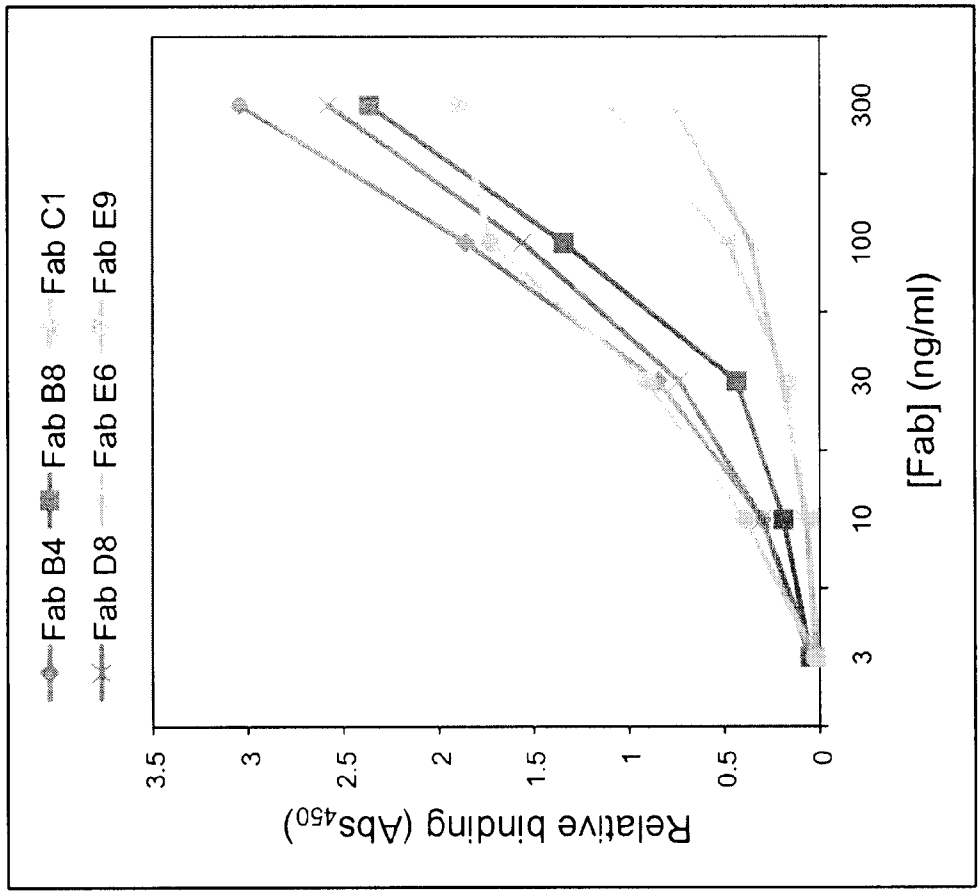

Fab B4
Fab B8
Fab C1
Fab D8
Fab E6
Fab E9
Relative binding (Abs450)
0
0.5
1
1.5
2
2.5
3
3.5
3
10
30
100
300
[Fab] (ng/ml)

FIGURE 7

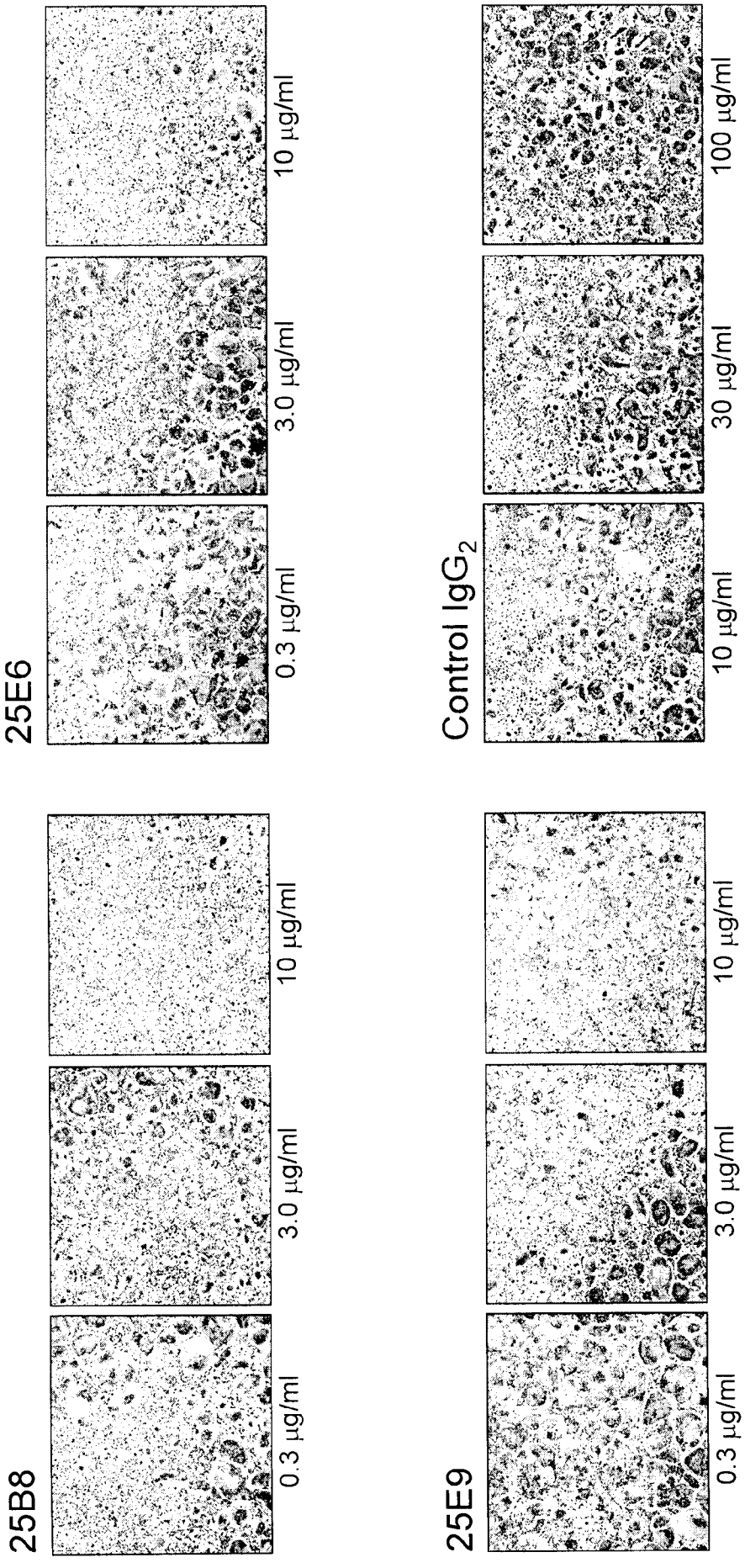
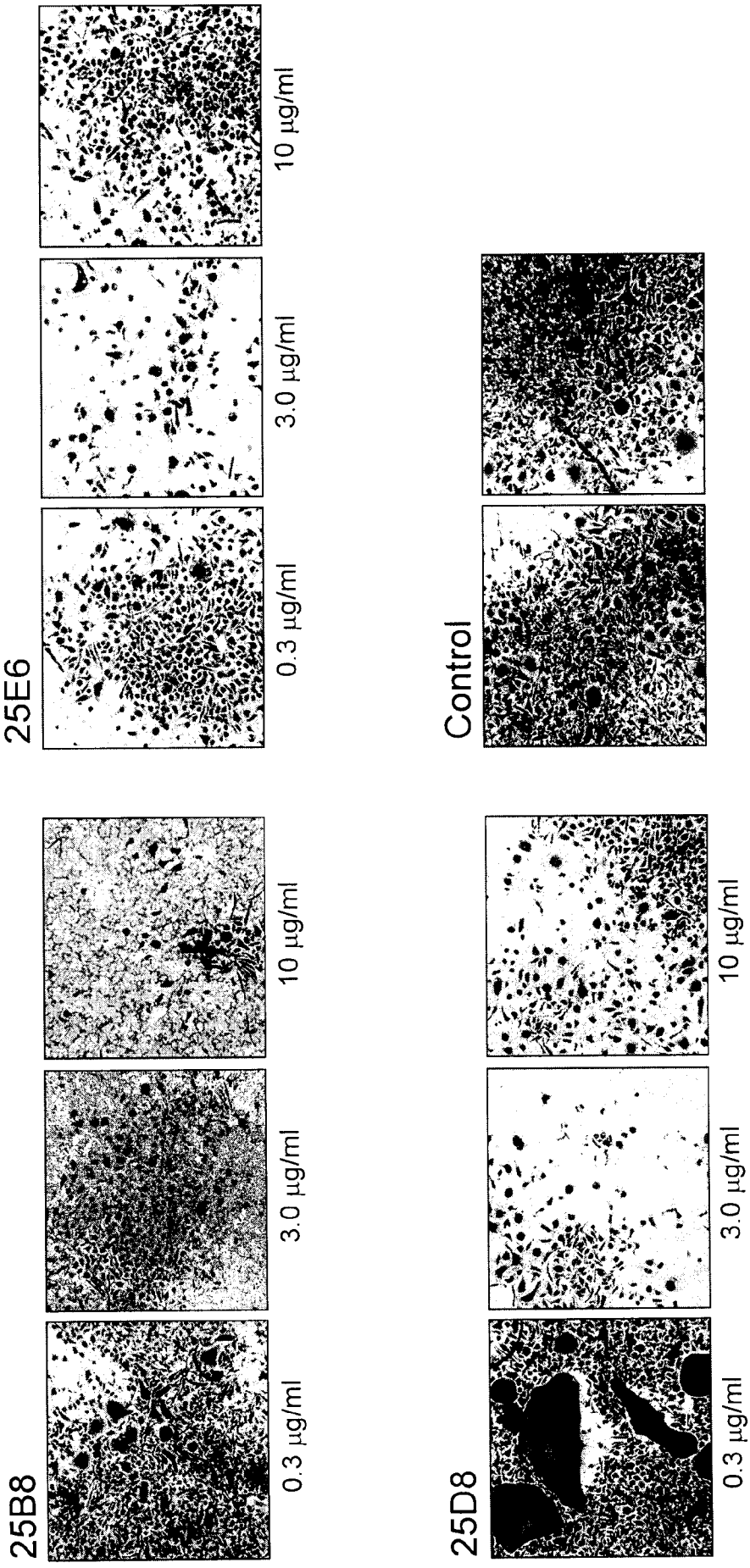

25B8
0.3 µg/ml
3.0 µg/ml
10 µg/ml
25E6
0.3 µg/ml
3.0 µg/ml
10 µg/ml
25E9
0.3 µg/ml
3.0 µg/ml
10 µg/ml
Control IgG2
10 µg/ml
30 µg/ml
100 µg/ml

FIGURE 8


25B8
0.3 µg/ml
3.0 µg/ml
10 µg/ml
25E6
0.3 µg/ml
3.0 µg/ml
10 µg/ml
Control
25D8
0.3 µg/ml
3.0 µg/ml
10 µg/ml

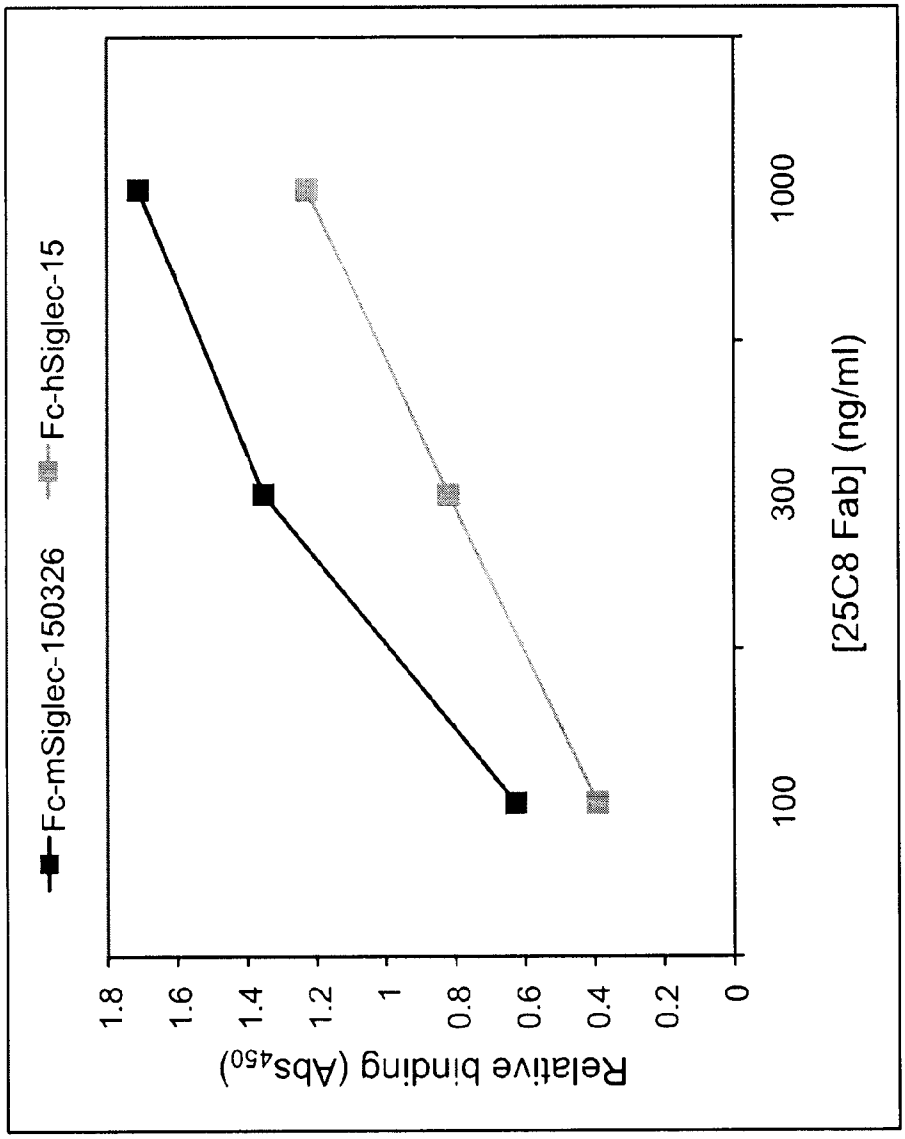

Fc-mSiglec-150326
Fc-hSiglec-15
Relative binding (Abs450)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
100
300
1000
[25C8 Fab] (ng/ml)

FIGURE 9

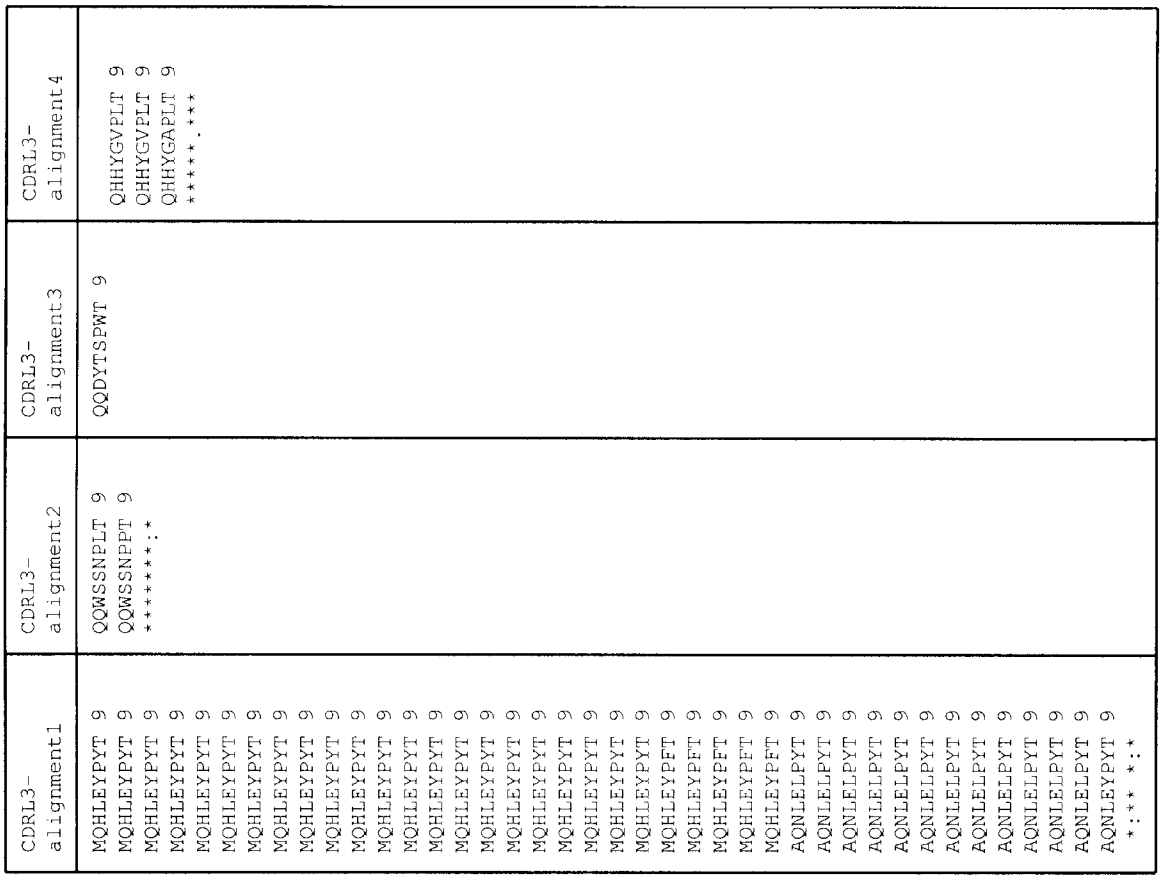
FIGURE 10A

CDRL1-alignment1	CDRL1-alignment2	CDRL1-alignment3	CDRL1-alignment4
RSSKSLLHSNGITYLY 16 RSSESLLHSNGITYLY 16 RSSKSLLHSNGVTYLY 16 RSSKSLLHSNGVTYLY 16 RSSKSLLHSNGVTYLY 16 RSTKSLLHSNGNTYLY 16 RSTKSLLHSNGNTYLY 16 RSTKSLLHSNGNTYLY 16 RSSKSLLHSNGNTYLY 16 RSSKSLLHSNGNTYLY 16 **::******* ****	SASSSVSYMY 10 SASSSVSYMY 10 **********	KASQSVSNAVA 11	RASGNIHNYLA 11 RASGNIHNYLA 11 RASENIYSYLA 11 *** **:.***

FIGURE 10B

CDRL2-alignment1	CDRL2-alignment2	CDRL2-alignment3	CDRL2-alignment4	CDRL2-alignment5
QMSNLAS 7 *******	QMSNLAS 7 RMSNLAS 7 RMSNLAS 7 RMSNLAS 7 RMSNLAS 7 RMSNLAS 7 :******	RMSNLAS 7 RMSNLAS 7 RMSNLAS 7 RMSNLAS 7 RMSNLAS 7 RTSNLAS 7 RTSNLVS 7 * ***.*	YTSNRYT 7	NAKTLPE 7 NAKTLPE 7 NAKTLAD 7 *****.:

FIGURE 10C



CDRL3-alignment1	CDRL3-alignment2	CDRL3-alignment3	CDRL3-alignment4
MQHLEYPYT 9	QQWSSNPLT 9	QQDYTSPWT 9	QHHYGVPLT 9
MQHLEYPYT 9	QQWSSNPPT 9		QHHYGVPLT 9
MQHLEYPYT 9	********:*		QHHYGAPLT 9
MQHLEYPYT 9			******.***
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPYT 9			
MQHLEYPFT 9			
MQHLEYPFT 9			
MQHLEYPFT 9			
MQHLEYPFT 9			
AQNLELPYT 9			
AQNLELPYT 9			
AQNLELPYT 9			
AQNLELPYT 9			
AQNLELPYT 9			
AQNLELPYT 9			
AQNLELPYT 9			
AQNLELPYT 9			
AQNLELPYT 9			
AQNLELPYT 9			
*:*** *:*			

FIGURE 11A

CDRH1- alignment	CDRH1- alignment 2	CDRH1- alignment3	CDRH1- alignment4
GYTFTDYDMH 10	GYTFTDYDMH	GFDFSKDWMS 10	GYTFTRNWIQ 10
GYTFTDYDMH 10	GYTFTDYDMH		GYTFTRNWIQ 10
GYTFTDYDMH 10	GYTFTDYDMH		GYTFTRNWIQ 10
GYTFTDYDMH 10	GYTFTDYDMH		**********
GYTFTDYEMH 10	GYTFTDYEMH		
GYTFTSYWMH 10	*******:**		
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTSYWMH 10			
GYTFTRYWMD 10			
GYTFTTYWMH 10			
GYTFTTYWMH 10			
GYTFTTYWMH 10			
GYTFTTYWMH 10			
GYTFTTYWMH 10			
GYTFNTYNMY 10			
****. * *			

FIGURE 11B

CDRH2-alignment1	CDRH2-alignment2	CDRH2-alignment3	CDRH2-alignment4	CDRH2-alignment5
LINPTNGRTN 10 LINPSNARTN 10 LINPSNARTN 10 LINPSNARTN 10 LINPSNARTN 10 LINPSNARTN 10 LINPSNARTN 10 LINPSNARTN 10 LINPSNGRPN 10 ****:*.*.*	TIDPETGGTA 10 TIDPETGGTA 10 TIDPETGGTA 10 TIDPETGGTA 10 AIDPETGGTA 10 :*********	EIDPSDSYTN 10 EINPDSSTIN 10 **:*..* *	GIDPSNGDTK 10	AIYPGNGDSR AIYPGNGDSR AVYPGNGDSR *:********

FIGURE 11C

CDRH3-alignment1	CDRH3-alignment2	CDRH3-alignment3	CDRH3-alignment4	CDRH3-alignment 5	CDRH3-alignment6
ARGGDGDYFDY 11 ***********	TSFYYTYSNYDVGFAY 16 TSFYYTYSNYDVGFAY 16 TSFYYTYSNYDVGFAY 16 TSFYYTYYNYDVGFAY 16 TTFYYSHYNYDVGFAY 16 *:***:: ********	ARSGAYSSDYSYDGFAY 17	SRLEDYEDWYFDV 13	TSHTY 5	ARLAGNYAYYFDY 13 ARLAGNYAYYFDY 13 ARLAGNYAYYFDY 13 *************

FIGURE 12

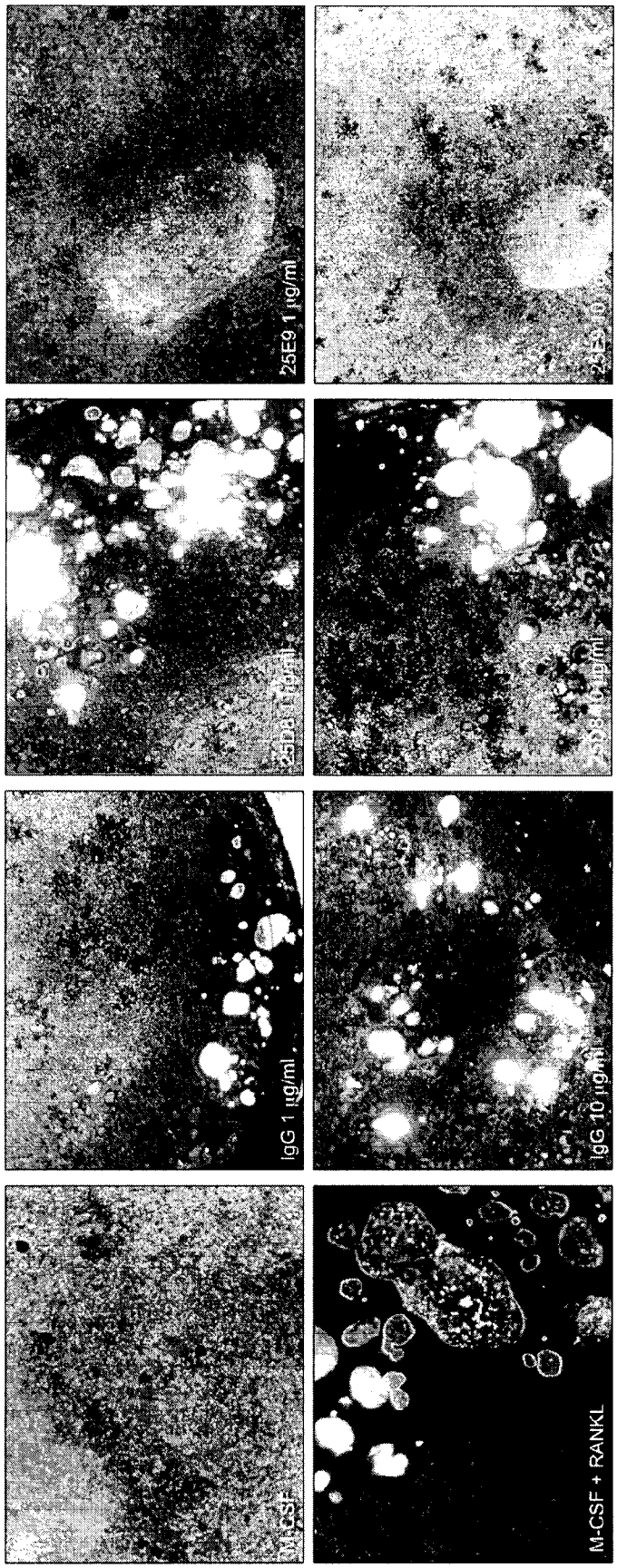


FIGURE 13

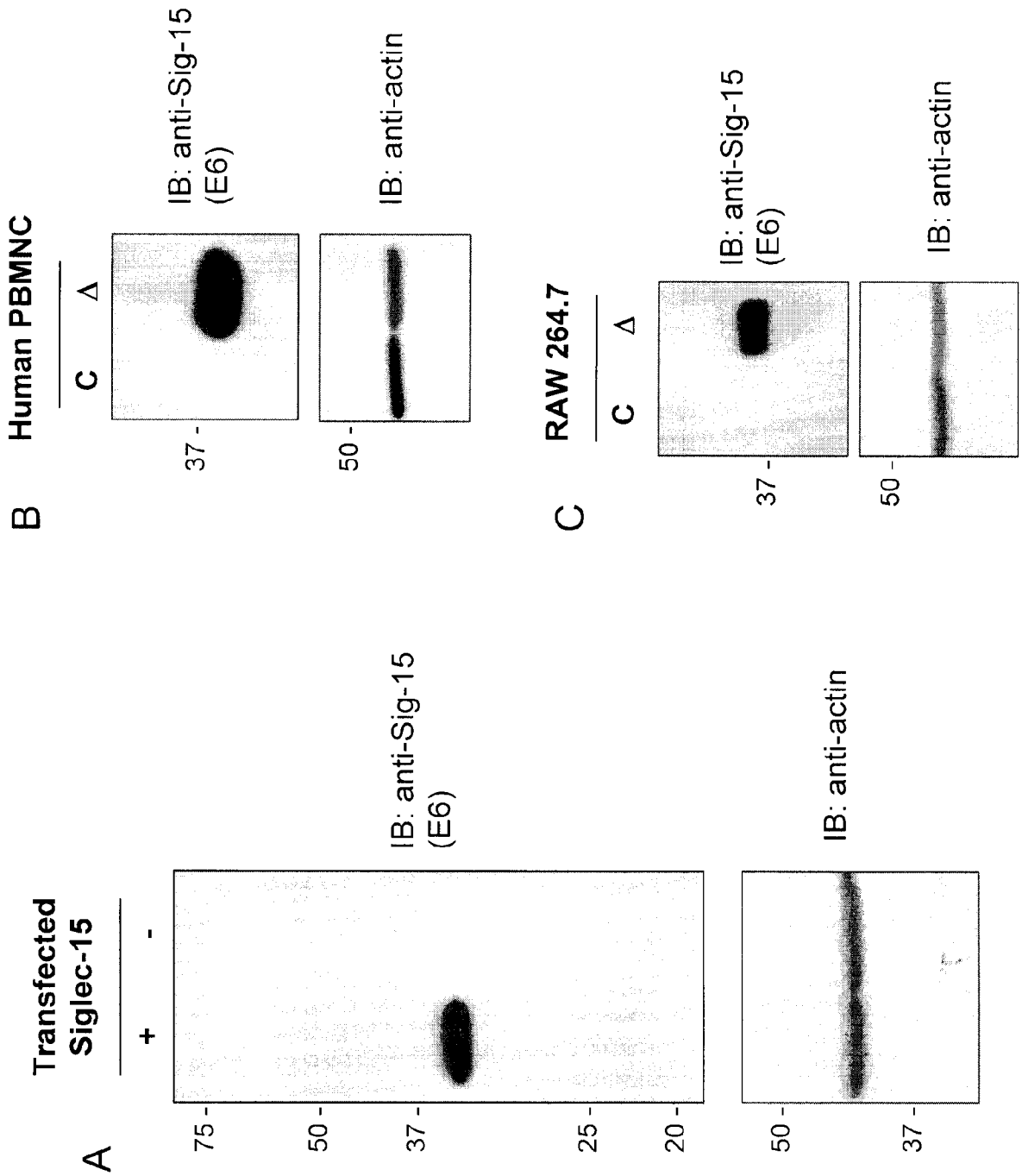

A
Transfected Siglec-15
+
-
IB: anti-Sig-15 (E6)
IB: anti-actin
75
50
37
25
20
50
37
B
Human PBMNC
C
Δ
IB: anti-Sig-15 (E6)
IB: anti-actin
37
50
C
RAW 264.7
C
Δ
IB: anti-Sig-15 (E6)
IB: anti-actin
37
50

FIGURE 13

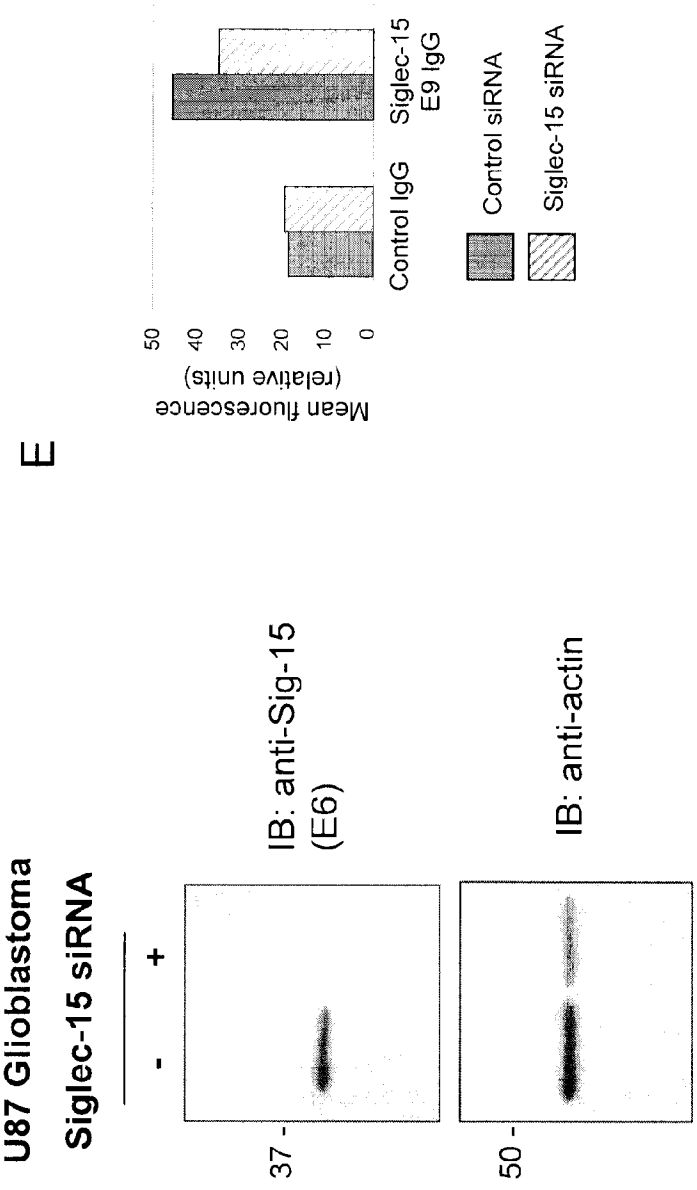

D
U87 Glioblastoma
Siglec-15 siRNA
-
+
IB: anti-Sig-15
(E6)
37 -
IB: anti-actin
50 -
E
Mean fluorescence
(relative units)
0
10
20
30
40
50
Control IgG
Siglec-15
E9 IgG
Control siRNA
Siglec-15 siRNA

FIGURE 14

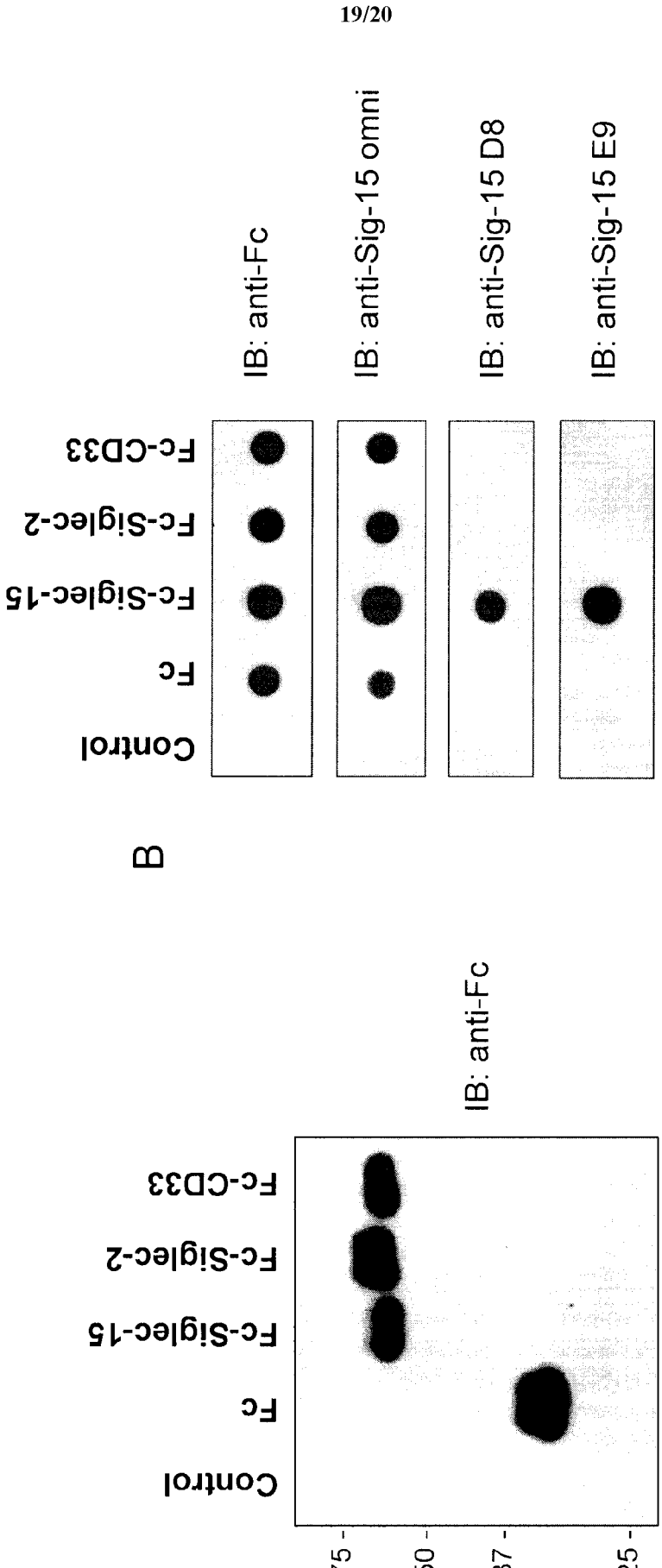
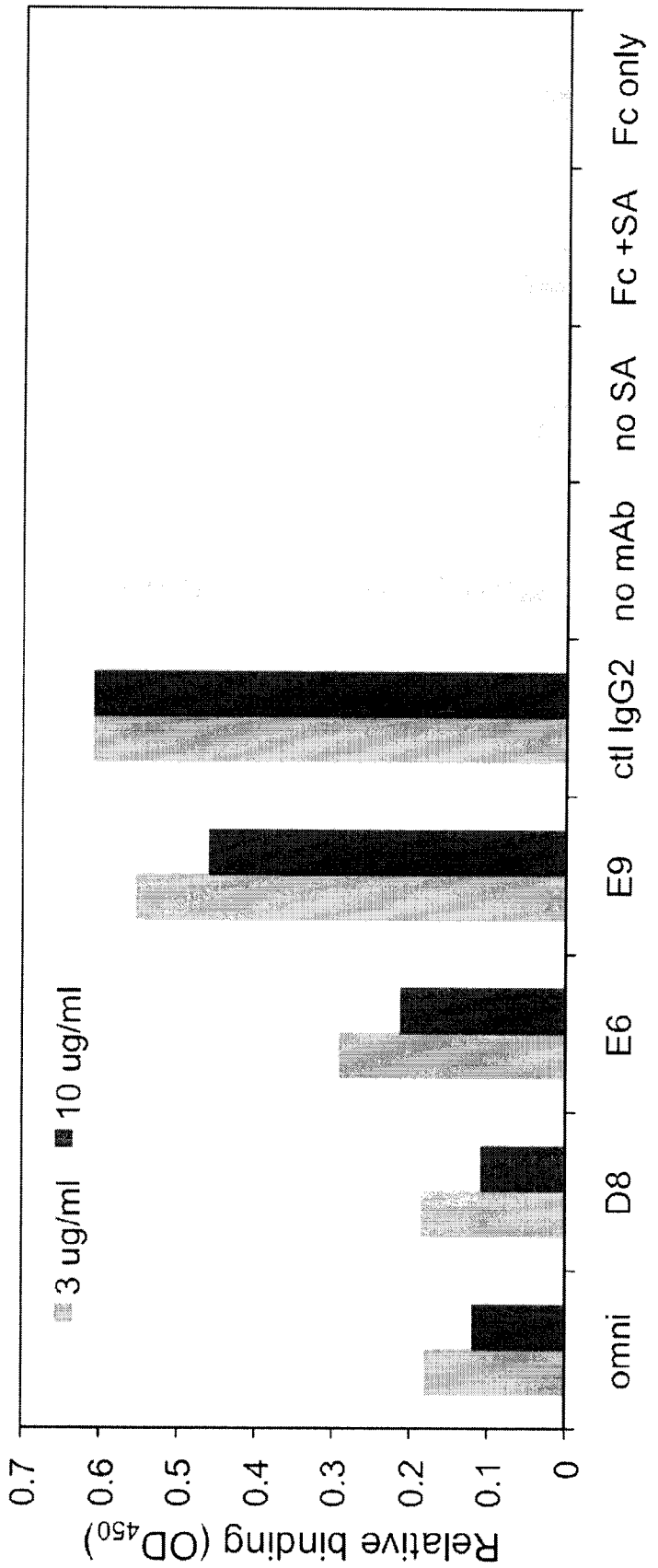

A
Control
Fc
Fc-Siglec-15
Fc-Siglec-2
Fc-CD33
IB: anti-Fc
75
50
37
25
B
Control
Fc
Fc-Siglec-15
Fc-Siglec-2
Fc-CD33
IB: anti-Fc
IB: anti-Sig-15 omni
IB: anti-Sig-15 D8
IB: anti-Sig-15 E9

FIGURE 15


Relative binding (OD450)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
3 ug/ml
10 ug/ml
omni
D8
E6
E9
ctl IgG2
no mAb
no SA
Fc +SA
Fc only
Primary antibody

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/001586

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07K 16/28*** (2006.01), ***A61K 31/7088*** (2006.01), ***A61K 31/713*** (2006.01), ***A61K 39/395*** (2006.01), ***A61K 49/00*** (2006.01), ***A61P 19/08*** (2006.01), ***A61P 35/00*** (2006.01), ***G01N 33/53*** (2006.01), ***G01N 33/574*** (2006.01), ***C12N 5/077*** (2010.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: ***C07K 16/28*** (2006.01), ***A61K 31/7088*** (2006.01), ***A61K 31/713*** (2006.01), ***A61K 39/395*** (2006.01), ***A61K 49/00*** (2006.01), ***A61P 19/08*** (2006.01), ***A61P 35/00*** (2006.01), ***G01N 33/53*** (2006.01), ***G01N 33/574*** (2006.01), ***C12N 5/077*** (2010.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Databases: Canadian Patent Database, EspaceNet, CAplus, Genome Quest, Scopus and Pubmed. **Keywords**: Siglec 15, CD33, like, sialic, immunoglobin, lectin, antibody, bone, resorption, osteoclast, differentiation, cancer, Alethia, Tremblay, Filion and Stuible.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2698326 A1 [WO 2009/048072 A1] (HIRUMA, Y & TSUDA, E) 16 April 2009 (16-04-2009) - Whole document -	1 - 24, 48 - 53, 60 - 65, 67, 71, 73 - 75 and 77 - 86
X	WO 2007/093042 A1 (SOOKNANAN, R. R. et al.) 23 August 2007 (23-08-2007) - page 33, line 33 - page 42, line 13; SEQ ID NO: 48, page 96; SEQ ID NO: 82, page 134; and pages 82 - 85 -	1 - 22, 24, 49 - 53, 60 - 65, 67, 71, 73 - 75, 81, 82, 84 and 85
E	WO 2010/117011 A1 (HIRUMA, Y et al.) 14 October 2010	

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2010 (10-12-2010)	18 January 2011 (18-01-2011)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Jacinth Abraham (819) 934-7598

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/001586

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 69, 70, 91 and 92

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 69, 70, 91 and 92 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 69, 70, 91 and 92.

2. [ ] Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2010/001586

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA 2698326 A1	16 April 2009 (16-04-2009)	AU2008311698A1	16 April 2009 (16-04-2009)
		EP2206727A1	14 July 2010 (14-07-2010)
		KR20100065153A	15 June 2010 (15-06-2010)
		MX2010003884A	30 April 2010 (30-04-2010)
		US2010209428A1	19 August 2010 (19-08-2010)
		WO2009/048072A1	16 April 2009 (16-04-2009)
WO 2007/093042 A1	23 August 2007 (23-08-2007)	AU2007215334A1	23 August 2007 (23-08-2007)
		CA2638823A1	23 August 2007 (23-08-2007)
		EP1994155A1	26 November 2008 (26-11-2008)
		EP1994155A4	12 August 2009 (12-08-2009)
		JP2009525730T	16 July 2009 (16-07-2009)
		US2009298763A1	03 December 2009 (03-12-2009)
		US2010104575A1	29 April 2010 (29-04-2010)

专利名称(译)	Siglec 15抗体治疗骨丢失相关疾病		
公开(公告)号	EP2486060A1	公开(公告)日	2012-08-15
申请号	EP2010821519	申请日	2010-10-06
[标]申请(专利权)人(译)	阿莱斯亚生物疗法股份有限公司		
申请(专利权)人(译)	ALETHIA生物治疗INC.		
当前申请(专利权)人(译)	ALETHIA生物治疗INC.		
[标]发明人	TREMBLAY GILLES BERNARD FILION MARIO STUIBLE MATTHEW		
发明人	TREMBLAY, GILLES BERNARD FILION, MARIO STUIBLE, MATTHEW		
IPC分类号	C07K16/28 A61K31/7088 A61K31/713 A61K39/395 A61K49/00 A61P19/08 A61P35/00 G01N33/53 G01N33/574 C12N5/077		
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摘要(译)

本文描述了特异性结合S？glec-15的新抗体和抗原结合片段。在一些实施方案中，抗体或抗原结合片段可以阻断S？glec-15的生物活性，并且可用于治疗骨丢失的组合物。更特别地，在具有增加的细胞表面表达的骨病中，例如破骨细胞的骨降解活性增加的病症本发明还涉及表达抗体或抗原结合片段如单克隆抗体的细胞。 ，人源化或嵌合抗体另外，还公开了使用抗体和片段检测和治疗骨丢失，骨相关疾病或癌症的方法。