SUMMARY OF THE ~~INVENTION~~DISCLOSURE

According to one aspect the present ~~invention~~disclosure provides a binding protein that dissociates from human RGM A (hRGM A) with a K_D of 1 x 10^{-7} M or less and a k_{off} rate constant of 1 x 10^{-2} s^{-1} or less, both determined by surface plasmon resonance.

According to another aspect the ~~invention~~disclosure relates to a binding protein, as for example a binding protein showing the above kinetic features, that binds to human RGM A and neutralizes the neurite outgrowth inhibitory activity of human RGM A as determined in a standard in vitro assay, as for example the Ntera neuronal outgrowth assay as exemplified in Example 3, below.

The ~~invention~~disclosure also relates to binding protein as defined above, having at least one of the following additional functional characteristics:

binding to rat RGM A,

binding to human RGM C, and

binding to rat RGM C.

In particular, the binding protein as described herein modulates the ability of RGM to bind to at least one of its receptors.

Such binding protein, in particular, binds to a receptor binding domain of human RGM A. For RGM A a N- and a C-terminal receptor binding domains have been identified. Particular embodiments of the binding proteins of the ~~invention~~disclosure bind to the N-terminal receptor binding domain of RGM A, as illustrated by the inhibition of binding between an N-terminal hRGM A fragment, as for example 47-168 and receptor molecules, like Neogenin and BMP-4. Said N-terminal hRGM A fragment may have a total length of about 30 to about 150 or about 30 to about 122 amino acid residues. As a non-limiting example Fragment 0 (corresponding to the N-terminal residues 47-168) of hRGM A as described herein or any shorter receptor binding fragment may be mentioned.

In particular said binding protein modulates, preferably inhibits, at least one of the following interactions:

binding of human RGM A to human BMP-4.

binding of hRGM A to human Neogenin,

binding of hRGM C to human Neogenin,

binding of human RGM A to human BMP-2.

According to a particular embodiment, the binding protein as herein defined is a humanized antibody.

The binding protein as described above may have an antigen binding domain, said binding protein capable of binding an epitope of an RGM molecule, said antigen binding domain comprising at least one CDR comprising an amino acid sequence selected from the group consisting of

GTTPDY (SEQ ID NO: 59),
FQATHDPLT (SEQ ID NO: 62),
ARRNEYYGSSFFDY (SEQ ID NO: 65),
LQGYIPPRT (SEQ ID NO: 68), and

modified CDR amino acid sequences having a sequence identity of at least 50% to one of said sequences. In another embodiment the present ~~invention~~disclosure relates to a binding protein, comprising an antigen binding domain, said binding protein being capable of binding an epitope of an RGM molecule, said antigen binding domain comprising at least one CDR comprising an amino acid sequence selected from the group consisting of:

GTTPDY (SEQ ID NO: 59),
FQATHDPLT (SEQ ID NO: 62),
ARRNEYYGSSFFDY (SEQ ID NO: 65),
LQGYIPPRT (SEQ ID NO: 68), and

modified CDR amino acid sequences having a sequence identity of at least 50%, as for example at least 55, 60, 65, 70, 75, 80, 85, 90, 95 % identity to one of said sequences.

For example, said binding protein may comprise two of said CDRs, as for example SEQ ID NO: 59 and 62; or SEQ ID NO: 65 and 68; wherein at least one of said CDRs may be modified, having a sequence identity of at least 50%, as for example at least 55, 60, 65, 70, 75, 80, 85, 90, 95 % identity to one of said sequences.

Said binding protein may further comprise at least one CDR comprise an amino acid sequence selected from the group consisting of SEQ ID NO: 57, 58, 60, 61, 63, 64, 66, 67 and modified CDR amino acid sequences having a sequence identity of at least 50%, as for example at least 55, 60, 65, 70, 75, 80, 85, 90, 95 % identity, to one of said sequences.

In particular, each of said above mentioned modifications may be generated by single or multiple amino acid addition, deletion, or, in particular, substitution, or combinations thereof.

In another embodiment, the binding protein comprises at least two variable domain CDR sets.

In particular, said at least two variable domain CDR sets are selected from a group consisting of:

VH 5F9 set& VL 5F9 set; and

VH 8D1 set & VL 8D1 set

The binding protein according to the ~~invention~~disclosure further comprising a human acceptor framework.

Said human acceptor framework may comprise at least one amino acid sequence selected from the group consisting of SEQ ID NO: 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 and 33.

The binding protein of the ~~invention~~disclosure may, in particular, comprise at least one set of framework sequences selected from the group consisting of the sets:

(1) VH3-48 set (Seq ID NO: 15, 16 and 17)

VH3-33 set (SEQ ID NO: 21, 22 and 23)

VH3-23 set (SEQ ID NO: 24, 25 and 26)

each of which sets being combined with a further framework sequence, selected from

JH3 (SEQ ID NO:18),

JH4 (SEQ ID NO:19),

JH6 (SEQ ID NO:20);

or

(2) selected from the group consisting of the sets

A18 set: (SEQ ID NO: 27, 28 and 29)

A17 set: (SEQ ID NO: 31, 32 and 33)

each of which sets being combined with a further framework sequence, selected from JK2 (SEQ ID NO:2)

According to particular embodiments, the binding protein of any one of the preceding claims comprising at least one CDR- grafted heavy chain variable domain

selected from SEQ ID NO: 35, 36, 37, 38, 39, 40, 41, 42, and 43; and/or at least one CDR-grafted light chain variable domain selected from SEQ ID NO: 44, 45, and 46.

More particular, the binding protein of the ~~invention~~disclosure comprises a combination of two variable domains, wherein said two variable domains have amino acid sequences selected from :

SEQ ID NOs: 35 & 44 ; 36 & 44 ; 37 & 44 ; 38 & 44 ; 39 & 44 ; 40 & 44 ; 41 & 44 ; 42 & 44 ; 43 & 44 ;

SEQ ID NOs: 35 & 45 ; 36 & 45 ; 37 & 45 ; 38 & 45 ; 39 & 45 ; 40 & 45 ; 41 & 45 ; 42 & 45 ; 43 & 45 ;

SEQ ID NOs: 35 & 46 ; 36 & 46 ; 37 & 46 ; 38 & 46 ; 39 & 46 ; 40 & 46 ; 41 & 46 ; 42 & 46 ; 43 & 46 ;

In another embodiment of the ~~invention~~disclosure, said human acceptor framework of the binding protein comprises at least one framework region amino acid substitution at a key residue, said key residue selected from the group consisting of:

a residue adjacent to a CDR;
a glycosylation site residue;
a rare residue;
a residue capable of interacting with a RGM epitope;
a residue capable of interacting with a CDR;
a canonical residue;
a contact residue between heavy chain variable region and light chain variable region;
a residue within a Vernier zone;
an N-terminal residue capable of paraglutamate formation and
a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework.

In particular, said key residues are selected from the group consisting
(heavy chain sequence position): 1, 5, 37, 48, 49, 88, 98
(light chain sequence position): 2, 4, 41, 51

In a particular embodiment, the binding protein of the ~~invention~~disclosure is or comprises a consensus human variable domain.

According to another embodiment of the binding protein of the ~~invention~~disclosure, said human acceptor framework comprises at least one framework region amino acid substitution, wherein the amino acid sequence of the framework is at least 65%, as for example at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99 %, identical to the sequence of said human acceptor framework and comprises at least 70 amino acid residues, as for example at least 75, 80, or 85 residues, identical to said human acceptor framework.

According to particular embodiment, the binding protein of the ~~invention~~disclosure comprises at least one framework mutated variable domain having an amino acid sequence selected from the group consisting of:

SEQ ID NO: 47, 48, 49, 50; (VH domain), and /or

selected from the group consisting of:

SEQ ID NO: 51, 52, 53, and 54 (VL domain)

In particular, said binding protein comprises two optionally framework mutated variable domains, wherein said two variable domains have amino acid sequences selected from the groups consisting of:

SEQ ID NOs: 47 & 44 ; 47 & 45 ; 47 & 46 ; 47 & 51 ; 47 & 52 ; 47 & 53 ; 47 & 54 ;

SEQ ID NOs: 48 & 44 ; 48 & 45 ; 48 & 46 ; 48 & 51 ; 48 & 52 ; 48 & 53 ; 48 & 54 ;

SEQ ID NOs: 49 & 44 ; 49 & 45 ; 49 & 46 ; 49 & 51 ; 49 & 52 ; 49 & 53 ; 49 & 54 ;

SEQ ID NOs: 50 & 44 ; 50 & 45 ; 50 & 46 ; 50 & 51 ; 50 & 52 ; 50 & 53 ; 50 & 54 ;

The binding proteins of the invention as described herein are capable of binding at least one target, selected from RGM molecules.

In particular, they are capable of binding to human RGM A, and optionally at least one further RGM molecule of human origin or originating from cynomolgus monkeys, rat, chick, frog, and fish.

For example they may additionally bind to rat RGM A, human RGM C, and /or rat RGM C.

In particular, the binding protein of the ~~invention~~disclosure is capable of modulating, in particular, capable of neutralizing or inhibiting a biological function of a target, selected from RGM molecules as defined above.

In particular, the binding protein of the ~~invention~~disclosure modulates, in particular inhibits, the ability of RGM to bind to at least one of its receptors, as for example Neogenin, and BMP, like BMP-2 and BMP-4.

For example said binding protein modulates , in particular diminishes and preferably inhibits at least one of the following interactions:

binding of human RGM A to human BMP-4.

binding of hRGM A to human Neogenin,

binding of hRGM C to human Neogenin,

binding of human RGM A to human BMP-2.

Binding proteins with different combinations of functional features, and consequently showing different functional profiles, as disclosed herein, are also within the scope of the ~~invention~~disclosure. Non-limiting examples of such profiles are listed below:

	Profiles																					
Feature	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Binding to human RGM A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Binding to rat RGM A	+	-	+	-	+	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+		+
Binding to human RGM C	+	-	-	-	-	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+	+
Binding to rat RGM C	+	-	-	-	-	-	-	-	-	-	+	+	+	+	-	-	-	-	+	+	+	+
Inhibition of binding of hRGM A to human Neogenin	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inhibition of binding of hRGM C to human Neogenin	+	-	-	-	-	+	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+
Inhibition of binding of human RGM A to human BMP-2	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inhibition of binding of human RGM A to human BMP-4	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

For example, profile 1 is met by antibody 5F9 as provided by the present ~~invention~~disclosure and its derivatives described herein.

For example, profile 2 is met by antibody 8D1 as provided by the present ~~invention~~disclosure and its derivatives as disclosed herein.

In particular, a binding protein of the ~~invention~~disclosure is capable of inhibiting at least one biological activity of RGM, in particular RGM A, wherein said RGM A is selected from human, cynomolgus monkeys, rat, chick, frog, and fish.

According to another embodiment the binding protein of the ~~invention~~disclosure has one or more of the following kinetic features:

(a) an on rate constant (k_{on}) to said target selected from the group consisting of: at least about $10^2 M^{-1}s^{-1}$; at least about $10^3 M^{-1}s^{-1}$; at least about $10^4 M^{-1}s^{-1}$; at least about $10^5 M^{-1}s^{-1}$; at least about $10^6 M^{-1}s^{-1}$, and at least about $10^7 M^{-1}s^{-1}$, as measured by surface plasmon resonance;

(b) an off rate constant (k_{off}) to said target selected from the group consisting of: at most about $10^{-2}s^{-1}$, at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance; or

(c) a dissociation constant (K_D) to said target selected from the group consisting of: at most about 10^{-7} M; at most about 10^{-8} M; at most about 10^{-9} M; at most about 10^{-10} M; at most about 10^{-11} M; at most about 10^{-12} M; and at most 10^{-13} M.

According to a further aspect, the present ~~invention~~disclosure provides an antibody construct comprising a binding protein described above, said antibody construct further comprising a linker polypeptide or an immunoglobulin constant domain.

Said antibody construct or binding protein of the ~~invention~~disclosure may be selected from the group consisting of: an immunoglobulin molecule, a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a Fab, a Fab', a F(ab')2, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, a dual variable domain immunoglobulin, and a bispecific antibody.

In an antibody construct according to the ~~invention~~disclosure said binding protein comprises a heavy chain immunoglobulin constant domain selected from the group consisting of;

a human IgM constant domain,

a human IgG1 constant domain,
a human IgG2 constant domain,
a human IgG3 constant domain,
a human IgG4 constant domain,
a human IgE constant domain,
a human IgD constant domain,
a human IgA1 constant domain
a human IgA2 constant domain
a human IgY constant domain and and
corresponding mutated constant domains

In particular, an antibody construct according to the ~~invention~~disclosure comprises an immunoglobulin constant domain having an amino acid sequence selected from the group consisting of: SEQ ID NO: 11, 12, 13 and 14

According to another aspect, the present ~~invention~~disclosure provides an antibody conjugate comprising an antibody construct described herein, said antibody conjugate further comprising an agent selected from the group consisting of; an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent, each of which agent being conjugated, of example covalently bound to said binding protein.

For example, said agent is an imaging agent selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin. In particular, said imaging agent is a radiolabel selected from the group consisting of: ^{3}H, ^{14}C, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I, ^{177}Lu, ^{166}Ho, and ^{153}Sm.

For example, said agent is a therapeutic or cytotoxic agent selected from the group consisting of; an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

According to another embodiment, said binding protein of the ~~invention~~disclosure as described herein possesses a human glycosylation pattern.

Furthermore, the binding proteins, antibody constructs and antibody conjugate according to the ~~invention~~disclosure may exist as a crystal (in crystalline form), preferably retaining biological activity.

In particular, said crystal is a carrier-free pharmaceutical controlled release crystal. In view of said crystalline form the binding protein, antibody construct or antibody conjugate may have a greater half life in vivo than the corresponding soluble counterpart

In another aspect of the present ~~invention~~disclosure provides an isolated nucleic acid encoding a binding protein amino acid sequence, antibody construct amino acid sequence, and antibody conjugate amino acid sequence as described herein.

The ~~invention~~disclosure also relates to a vector comprising an isolated nucleic acid as described herein. In particular, the vector is selected from the group consisting of pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, and pBJ.

The ~~invention~~disclosure also relates to a host cell comprising each a vector. In particular, said host cell is a prokaryotic cell, as for example E.coli; or is a eukaryotic cell, and may be selected from the group consisting of protist cell, animal cell, plant cell and fungal cell. In particular, said eukaryotic cell is an animal cell selected from the group consisting of; a mammalian cell, an avian cell, and an insect cell. Preferably said host cell is selected from HEK cells, CHO cells, COS cells and yeast cells. The yeast cell may be *Saccharomyces cerevisiae* and said insect cell ay be a Sf9 cell.

The ~~invention~~disclosure also provides a method of producing a protein capable of binding RGM, comprising culturing a host cell as defined herein in culture medium under conditions sufficient to produce a binding protein capable of binding RGM.

The ~~invention~~disclosure also relates to a protein produced according to said method.

The ~~invention~~disclosure also provides a composition for the release of a binding protein said composition comprising

(a) a formulation, wherein said formulation comprises a crystallized product protein as defined herein, and an ingredient; and

(b) at least one polymeric carrier.

Said polymeric carrier may be a polymer selected from one or more of the group consisting of: poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (b-hydroxybutryate), poly (caprolactone), poly (dioxanone); poly (ethylene glycol), poly ((hydroxypropyl) methacrylamide, poly [(organo) phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride- alkyl vinyl ether copolymers, pluronic polyols,

albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polyeaccharides, blends and copolymers thereof.

Said ingredient may be selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-ß- cyclodextrin, methoxypolyethylene glycol and polyethylene glycol.

According to another aspect the present ~~invention~~disclosure provides a method for treating a mammal comprising the step of administering to the mammal an effective amount of the composition as defined herein.

According to another aspect the present ~~invention~~disclosure provides a pharmaceutical composition comprising the product (in particular, a binding protein, construct or conjugate as scribed herein above), and a pharmaceutically acceptable carrier.

Said pharmaceutically acceptable carrier may function as adjuvant useful to increase the absorption, or dispersion of said binding protein.

For example said adjuvant is hyaluronidase.

According to another embodiment said pharmaceutical further comprises at least one additional therapeutic agent for treating a disorder in which RGM activity is detrimental. For example said agent is selected from the group consisting of: therapeutic agent, imaging agent, cytotoxic agent, angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; cyclosporin; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an antirheumatic; a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

The present ~~invention~~disclosure also relates to a method for reducing human RGM A activity comprising contacting human RGM A with at least one product (in particular, a binding protein, construct or conjugate as scribed herein above), such that at least one human RGM A activity is reduced.

The present ~~invention~~disclosure also relates to a method for decreasing hRGM A binding to Neogenin receptor in a subject in need thereof, comprising the step of administering to the subject a product of the ~~invention~~disclosure (in particular, a binding protein, construct or conjugate as scribed herein above).

The present ~~invention~~disclosure also relates to a method for decreasing hRGM A binding to bone morphogenetic protein-2 and/or bone morphogenetic protein-4 (BMP-2 and BMP-4) in a subject in need thereof, comprising the step of administering to the subject a product of the ~~invention~~disclosure (in particular, a binding protein, construct or conjugate as scribed herein above).

The present ~~invention~~disclosure also relates to a method for treating a subject for a disorder associated with RGM A activity comprising the step of administering alone or in combination with other therapeutic agents a product of the ~~invention~~disclosure (in particular, a binding protein, construct or conjugate as described herein above).

The present ~~invention~~disclosure also relates to a method for reducing RGM A activity in a subject suffering from a disorder in which RGM A activity is detrimental, comprising administering to the subject a product of the ~~invention~~disclosure (in particular, a binding protein, construct or conjugate as scribed herein above), alone or in combination with other therapeutic agents.

Said disorder preferably comprises neurological diseases selected from the group comprising Amyotrophic Lateral Sclerosis, Brachial Plexus Injury, Brain Injury, including traumatic brain injury, Cerebral Palsy, Guillain Barre, Leukodystrophies, Multiple Sclerosis, Post Polio, Spina Bifida, Spinal Cord Injury, Spinal Muscle Atrophy, Spinal Tumors, Stroke, Transverse Myelitis; dementia, senile dementia, mild cognitive impairment, Alzheimer-related dementia, Huntington's chorea, tardive dyskinesia, hyperkinesias, manias, Morbus Parkinson, steel-Richard syndrome, Down's syndrome, myasthenia gravis, nerve trauma, vascular amyloidosis, cerebral hemorrhage I with amyloidosis, brain inflammation, acute confusion disorder, amyotrophic lateral sclerosis, glaucoma and Alzheimer's disease.

Further particular aspects of the ~~invention~~disclosure are described below:

An isolated binding protein that specifically interacts with at least one epitope of a hRGM A protein;

In a first aspect, there is provided a monoclonal antibody comprising an antigen binding domain, said antibody capable of binding an epitope of a RGM molecule, said antigen binding domain comprising a heavy chain variable domain having at least three complementary determining regions and a light chain variable domain having at least three complementary determining regions, wherein the at least three complementary determining regions of the heavy chain variable domain have the amino acid sequence of SEQ ID NO:57, SEQ ID NO:58 and SEQ ID NO:59 and the at least three complementary determining regions of the light chain variable domain have the amino acid sequence of SEQ ID NO: 60, SEQ ID NO:61 and SEQ ID NO:62.

In a second aspect, there is provided an antigen binding fragment of the antibody as defined herein.

In a third aspect, there is provided a pharmaceutical composition comprising the antibody as defined herein and a pharmaceutically acceptable carrier.

CLAIMS

1. An isolated antibody comprising an antigen binding domain, said antibody capable of binding an epitope of a RGM molecule, said antigen binding domain comprising a heavy chain variable domain having at least three complementary determining regions and a light chain variable domain having at least three complementary determining regions, wherein the at least three complementary determining regions of the heavy chain variable domain have the amino acid sequence of SEQ ID NO:57, SEQ ID NO:58 and SEQ ID NO:59 and the at least three complementary determining regions of the light chain variable domain have the amino acid sequence of SEQ ID NO: 60, SEQ ID NO:61 and SEQ ID NO:62.

2. The antibody of claim 1, wherein said antibody further comprises a human acceptor framework, wherein said human acceptor framework comprises at least one amino acid sequence selected from the group consisting of: SEQ ID NO: 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 and 33.

3. An antigen binding fragment of the antibody of claim 1.

4. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition comprising the antibody of claim 2 and a pharmaceutically acceptable carrier.

6. An isolated antibody comprising an antigen binding domain, said antibody capable of binding an epitope of a RGM molecule, said antigen binding domain comprising a heavy chain variable domain having at least three complementary determining regions and a light chain variable domain having at least three complementary determining regions, wherein the at least three complementary determining regions of the heavy chain variable domain have the amino acid sequence of SEQ ID NO:63, SEQ ID NO:64 and SEQ ID NO:65 and the at least three complementary determining regions of the light chain variable domain have the amino acid sequence of SEQ ID NO: 66, SEQ ID NO:67 and SEQ ID NO:68.

7. The antibody of claim 6, wherein said antibody further comprises a human acceptor framework, wherein said human acceptor framework comprises at least one amino acid sequence selected from the group consisting of: SEQ ID NO: 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 and 33.

8. An antigen binding fragment of the antibody of claim 6.

9. A pharmaceutical composition comprising the antibody of claim 6 and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising the antibody of claim 7 and a pharmaceutically acceptable carrier.

11. An isolated antibody comprising an antigen binding domain, said antibody capable of binding an epitope of a RGM molecule, said antigen binding domain comprising a heavy chain variable domain and a light chain variable wherein the heavy chain variable domain has the amino acid sequence selected from the group consisting of: SEQ ID NOS: 35, 36, 37, 38, 39, 40, 41, 42, 43, 47, 48, 49 and 50 and wherein the light chain variable domain has the amino acid sequence selected from the group consisting of SEQ ID NO:44, 45, 46, 51, 52, 53 and 54.

12. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:35 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

13. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:36 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

14. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:37 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

15. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:38 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

16. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:39 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

17. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:40 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

18. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:41 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

19. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:42 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

20. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:43 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

21. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:35 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

22. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:36 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

23. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:37 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

24. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:38 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

25. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:39 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

26. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:40 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

27. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:41 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

28. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:42 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

29. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:43 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

30. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:35 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

31. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:36 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

32. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:37 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

33. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:38 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

34. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:39 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

35. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:40 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

36. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:41 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

37. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:42 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

38. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:43 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

39. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:44.

40. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:45.

41. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:46.

42. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:51.

43. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:52.

44. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:53.

45. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:54.

46. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:44.

47. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:45.

48. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:46.

49. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:51.

50. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:52.

51. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:53.

52. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:54.

53. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:49 and the light chain variable domain has the amino acid sequence of SEQ ID NO:44.

54. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:44.

55. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:49 and the light chain variable domain has the amino acid sequence of SEQ ID NO:45.

56. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:45.

57. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:49 and the light chain variable domain has the amino acid sequence of SEQ ID NO:46.

58. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:46.

59. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:51.

60. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:52.

61. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:53.

62. The antibody of claim 11, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:54.

63. A pharmaceutical composition comprising the antibody of claims 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40,

41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61 or 62 and a pharmaceutically acceptable carrier.

64. The antibody of claim 1, wherein the antibody is a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a multispecific antibody, a dual specific antibody or a bispecific antibody.

65. The antibody of claim 2, wherein the antibody is a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a multispecific antibody, a dual specific antibody or a bispecific antibody.

66. The antibody of claim 6, wherein the antibody is a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a multispecific antibody, a dual specific antibody or a bispecific antibody.

67. The antibody of claim 7, wherein the antibody is a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a multispecific antibody, a dual specific antibody or a bispecific antibody.

68. The antibody of claim 11, wherein the antibody is a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a multispecific antibody, a dual specific antibody or a bispecific antibody.

CLAIMS

1. A monoclonal antibody comprising an antigen binding domain, said antibody capable of binding an epitope of a RGM molecule, said antigen binding domain comprising a heavy chain variable domain having at least three complementary determining regions and a light chain variable domain having at least three complementary determining regions, wherein the at least three complementary determining regions of the heavy chain variable domain have the amino acid sequence of SEQ ID NO:57, SEQ ID NO:58 and SEQ ID NO:59 and the at least three complementary determining regions of the light chain variable domain have the amino acid sequence of SEQ ID NO: 60, SEQ ID NO:61 and SEQ ID NO:62.

2. The antibody of claim 1, wherein said antibody further comprises a human acceptor framework, wherein said human acceptor framework comprises at least one amino acid sequence selected from the group consisting of: SEQ ID NO: 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32 and 33.

3. An antigen binding fragment of the antibody of claim 1.

4. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition comprising the antibody of claim 2 and a pharmaceutically acceptable carrier.

6. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence selected from the group consisting of: SEQ ID NOS: 35, 36, 37, 38, 39, 40, 41, 42, 43, 47, 48, 49 and 50 and wherein the light chain variable domain has the amino acid sequence selected from the group consisting of SEQ ID NO:44, 45, 46, 51, 52, 53 and 54.

7. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:35 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

8. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:36 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

9. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:37 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

10. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:38 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

11. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:39 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

12. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:40 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

13. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:41 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

14. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:42 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

15. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:43 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 44.

16. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:35 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

17. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:36 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

18. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:37 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

19. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:38 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

20. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:39 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

21. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:40 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

22. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:41 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

23. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:42 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

24. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:43 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 45.

25. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:35 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

26. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:36 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

27. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:37 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

28. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:38 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

29. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:39 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

30. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:40 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

31. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:41 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

32. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:42 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

33. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:43 and the light chain variable domain has the amino acid sequence of SEQ ID NO: 46.

34. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:44.

35. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:45.

36. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:46.

37. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:51.

38. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:52.

39. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:53.

40. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:47 and the light chain variable domain has the amino acid sequence of SEQ ID NO:54.

41. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:44.

42. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:45.

43. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:46.

44. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:51.

45. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:52.

46. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:53.

47. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:48 and the light chain variable domain has the amino acid sequence of SEQ ID NO:54.

48. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:49 and the light chain variable domain has the amino acid sequence of SEQ ID NO:44.

49. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:44.

50. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:49 and the light chain variable domain has the amino acid sequence of SEQ ID NO:45.

51. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:45.

52. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:49 and the light chain variable domain has the amino acid sequence of SEQ ID NO:46.

53. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:46.

54. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:51.

55. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:52.

56. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:53.

57. The antibody of claim 1, wherein the heavy chain variable domain has the amino acid sequence of SEQ ID NO:50 and the light chain variable domain has the amino acid sequence of SEQ ID NO:54.

58. A pharmaceutical composition comprising the antibody of any one of claims 6-57 and a pharmaceutically acceptable carrier.

59. The antibody of claim 1, wherein the antibody is a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a multispecific antibody, a dual specific antibody or a bispecific antibody.

60. The antibody of claim 2, wherein the antibody is a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a multispecific antibody, a dual specific antibody or a bispecific antibody.

61. The antibody of claim 6, wherein the antibody is a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a multispecific antibody, a dual specific antibody or a bispecific antibody.