TREATMENT OF DISEASES WITH MONOCLONAL ANTIBODY DRUGS AND MOLECULAR DEGRADERS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial No. 63/634,719, filed on April 16, 2024, and U.S. Provisional Application Serial No. 63/721,522, filed on November 17, 2024, the contents of both of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

[0001] The application generally relates to a method of treating an immunology or inflammatory disease or condition. The application also relates to a method of restoring the therapeutic activity of a monoclonal antibody drug in a patient who has developed anti-drug antibodies.

BACKGROUND

[0002] Various diseases are associated with elevated levels of certain proteins in circulation. For example, increased levels of multiple circulating pro-inflammatory cytokines (i.e., signaling proteins that promote inflammatory effect) contribute to a variety of systemic inflammatory conditions and autoimmune diseases. In particular, increased levels of cytokines such as tumor necrosis factor alpha (TNFα) are associated with rheumatoid arthritis (RA), atherosclerosis and other diseases.

[0003] Autoimmune or inflammatory diseases including RA may be treated with TNFα inhibitors and other biologics. However, these inhibitors and biologics are protein drugs that tend to induce an immune response against themselves (immunogenicity), particularly the formation of anti-drug antibodies (ADAs).

[0004] There are two types of ADAs commonly associated with biologic therapies – non-neutralizing ADAs and neutralizing ADAs. Non-neutralizing ADAs (or binding antibodies, BAb) bind to a therapeutic protein but not at the target-binding site, potentially leading to reduced drug efficacy and increased clearance. Neutralizing ADAs (NAb) inhibit the biological activity of the therapeutic protein through interruption of target binding. Therefore, ADAs can alter a drug's pharmacokinetic (PK) and pharmacodynamics (PD) properties, reducing drug efficacy. For example, TNFα inhibitors and other biologic disease-modifying antirheumatic drugs (bDMARDs) do not achieve sustained remission in a large

proportion of patients due to the development of ADAs. Accordingly, there remains a need for new therapies to treat autoimmune or inflammatory diseases. It would be a further advantage if the new therapies can restore therapeutic effects of biologics in patients who have developed ADAs.

SUMMARY

[0005] In an aspect, a method of treating a disease or a condition in a patient in need thereof includes administering to the patient an immunoglobulin G degrader and a monoclonal antibody drug, wherein the immunoglobulin G degrader is effective to bind to an anti-drug antibody induced by the monoclonal antibody drug.

[0006] In another aspect, a method of restoring a therapeutic activity of a monoclonal antibody drug in a patient includes administering to the patient a therapeutically effective amount of an immunoglobulin G degrader, wherein the immunoglobulin G degrader is effective to bind to an anti-drug antibody induced by the monoclonal antibody drug.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The following descriptions should not be considered limiting in any way.

[0008] FIG. 1 is a plot of immunoglobulin (IgG) percentage relative to baseline (% IgG) over time (days) after administration of Compound 1 IgG degrader in a non-human primate (NHP), and shows that a single dose of the IgG degrader can lead to 80% IgG reduction in two to three days;

[0009] FIG. 2 is a plot of IgG percentage relative to baseline (% IgG) over time after administration of Compound 1 IgG degrader in a cynomolgus monkey (cyno), and shows that the depth of IgG lowering can reach 90% after second dose of the IgG degrader;

[0010] FIG. 3 is a plot of the fluorescent area (square micrometer per image, μm^2/image) versus the concentration of anti-adalimumab antibodies (nM) at various hours after the administration of Compound 1 IgG degrader, and shows that the IgG degrader binds and degrades anti-adalimumab antibodies in vitro;

[0011] FIG. 4 is a plot of the mean concentration of adalimumab (microgram per milliliter, µg/mL) over time (days) after starting the administration of adalimumab, wherein the adalimumab is administered without prior IgG treatment or administered 2 hours or 12 hours after a prior treatment with Compound 1 IgG degrader, and shows that the IgG degrader is compatible with biologic therapeutics when dosed ≥ 12 hours prior;

[0012] FIG. 5 is a plot of ADA titer (arbitrary unit, AU) over time (hours), and shows that ADAs induced by the administered adalimumab are reduced > 80% at 48 hours with a single dose of Compound 1 IgG degrader; and

[0013] FIG. 6 is a plot of TNFα neutralization activity of adalimumab versus vehicle (%) over time (hours), showing that Compound 1 IgG degrader restores adalimumab activity through ADA removal.

DETAILED DESCRIPTION

[0014] The following detailed description is provided to aid those skilled in the art in practicing the present invention. Those of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present disclosure.

Terminology

[0015] Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this application belongs. However, if a term in the present application contradicts or conflicts with a term in the incorporated reference, the term from the present application takes precedence over the conflicting term from the incorporated reference.

[0016] All ranges disclosed herein are inclusive of the endpoints, and the endpoints are independently combinable with each other.

[0017] The terms "a" and "an" and "the" do not denote a limitation of quantity and are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context.

[0018] "Or" means "and/or" unless clearly stated otherwise.

[0019] A "combination thereof" is open and includes any combination comprising at least one of the listed components or conditions optionally together with a like or equivalent component or condition not listed.

[0020] Unless otherwise indicated, any reference to a compound herein by structure, name, or any other means includes pharmaceutically acceptable salts; alternate solid forms, such as polymorphs, solvates, and hydrates, etc.

[0021] If stereochemistry is not indicated, a name or structural representation includes any stereoisomer or any mixture of stereoisomers.

[0022] "Pharmaceutically acceptable salt" includes derivatives of the disclosed compounds wherein the parent compound is modified by making salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, inorganic or organic acid salts of basic residues such as amines. For example, acid salts can include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid and the like; as well as those derived from organic acids such as acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, pamoic acid, maleic acid, hydroxylmaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, mesylic acid, esylic acid, besylic acid, sulfanilic acid, 2- acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethane disulfonic acid, oxalic acid, isethionic acid, $HOOC\text{-}(CH_2)_n\text{-}COOH$ where n is 0-4, and the like. Lists of additional suitable salts may be found, e.g., in G. Steffen Paulekuhn, et al., Journal of Medicinal Chemistry 2007, 50, 6665 and Handbook of Pharmaceutically Acceptable Salts: Properties, Selection and Use, P. Heinrich Stahl and Camille G. Wermuth Editors. Wiley-VCH, 2002.

[0023] The term "carrier" applied to pharmaceutical compositions of the disclosure refers to an excipient, diluent, or vehicle with which an active compound or biologics (e.g., an IgG degrader or a monoclonal antibody drug) is provided. A "pharmaceutically acceptable carrier" means a substance, e.g., excipient, diluent, or vehicle, that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable carrier" includes both one and more than one such carrier.

[0024] A "patient" or a "subject" is a human or non-human animal. The term "non-human animal" includes, for example, vertebrates such as non-human primates, horses, livestock such as sheep and cows, pets such as dogs and cats, and rodents such as mice, rats and guinea pigs. In some embodiments, the patent or the subject is a human.

[0025] "Treatment" or "treating" means alleviating, inhibiting, ameliorating, relieving, reducing, and/or slowing a condition or a disease in a subject.

[0026] The term "therapeutically effective amount" is the amount sufficient to effect treatment, as defined herein, when administered to a patient or a subject in need of such treatment.

[0027] "Administering" or "administration" means giving, providing, applying, or dispensing by any suitable route.

[0028] "Administered in combination" of an IgG degrader and a monoclonal antibody drug or " combination treatment" involving an IgG degrader and a monoclonal antibody includes administration of the individual therapeutic agents separately, or administration of the individual therapeutic agents sequentially by any suitable route, or a combination thereof. The dosage of the individual therapeutic agents may require more frequent administration of one of the therapeutic agents as compared to the other administered therapeutic agent. Therefore, to permit appropriate dosing, packaged pharmaceutical products may contain one or more dosage forms that contain one of therapeutic agents, but not the other co-administered therapeutic agent.

Combination Treatment with IgG degraders and monoclonal antibody drugs

[0029] Immunoglobulin G (IgG) is an antibody that plays a key role in defending the body against infections. However, in autoimmune disorders, elevated IgG levels can lead to the immune system mistakenly attacking the body's own healthy cells.

[0030] The neonatal Fc receptor (FcRn) is involved in the distribution, transport, and persistence of IgG. FcRn inhibitors bind to FcRn and prevent it from interacting with IgG antibodies, which can lead to the degradation of IgG and the reduction of its levels in the blood.

[0031] Unlike the existing IgG lowing therapies that use FcRn inhibitors, the IgG degrader disclosed herein is a bifunctional molecule that can target and then deliver pathogenic IgG autoantibodies, immune complexes to asialoglycoprotein receptors (ASPR) on hepatocytes for internalization and lysosomal degradation. The IgG degrader represents an entirely novel mechanistic class of agents for the treatment of IgG autoantibody-mediated diseases including RA. Compared to FcRn inhibitors, the IgG degrader provides deep, tunable IgG degradation, with dosage and frequency adjustments allowing for customizable treatment.

[0032] The IgG degrader can have a clean safety profile, with no serious adverse events and no significant changes in liver function tests. The IgG degrader can also be subcutaneously self-administered.

[0033] In addition, the inventors found that due to its fast clearance the IgG degrader as disclosed herein can be administered in combination with monoclonal antibody drugs such as a Fc-containing biologics, as the IgG degrader does not adversely affect the PK of these biologics. The IgG degrader can also reduce ADAs that have formed against the biologics, thus restoring their earlier beneficial effects. The IgG degrader can bind to a binary complex

formed between the anti-drug antibody and the monoclonal antibody drug to form a ternary complex, which is then degraded through asialoglycoprotein receptors of hepatocytes. Moreover, the IgG degrader can bind to a binary complex formed between TNFα and monoclonal antibody drug to form a ternary complex and facilitate TNFα's removal from circulation by binding and degrading the ternary complex through asialoglycoprotein receptors of hepatocytes. In other words, IgG itself can have therapeutic effects due to the removal of TNFα. Thus, the IgG degrader offers a unique combinatorial therapeutic approach for difficult to treat autoimmune or inflammatory diseases or conditions.

[0034] The benefits that are offered by the IgG degrader versus FcRn inhibitors as summarized in Table 1.

	FcRn inhibitors	IgG degrader
No impact on AEs of interest	Hypoalbuminemia, dyslipidemia, headache	None expected
No impact on Host Defense (IgG_3)	Lowers IgG_3	IgG_3-sparing
Accelerated Time to Peak Effect (IgG lowering)	5-22 days	24-48 hours
Advantageous drug exposure window	Continuous	Only ~ 24 hours (Degrader is rapidly cleared)
Immunogenicity	Emerging issues	None expected
Ability to dose on demand for disease flares or deeper LgG Lowering	Mechanistically impossible	Allowed
Convenient & Preferred Dosing	SC/IV infusion by health professional	Anticipated SC self-administered
Ability to administer with Fc-containing biologics	Precluded per label/MOA	Allowed (the IgG degrader can be rapidly cleared)

AE: adverse effect
SC: subcutaneous

[0035] In an aspect, the application is directed to a method of treating a disease or a condition in a patient in need thereof. The method comprises a combination treatment, which comprises administering to the patient an IgG degrader and a monoclonal antibody (mAb) drug, wherein the IgG degrader is effective to bind to an anti-drug antibody (ADA) induced by the mAb.

[0036] As used herein "the anti-drug antibody induced by the monoclonal antibody drug" refers to the antibody generated by the patient's immune system in response to the administration of the mAb. The anti-drug antibody can include a neutralizing antibody, a binding antibody, or a combination thereof.

[0037] "Effective to bind to an anti-drug antibody" means that the IgG degrader is capable of binding to the ADA, for example, forming a protein complex that then binds asialoglycoprotein receptors on hepatocytes and is subsequently internalized and degraded in hepatic lysosomes. As a consequence of this mechanism, the ADA is eliminated from circulation by hepatocytes, thus resulting in lowered level of the ADA.

[0038] As discussed herein, ADAs can alter the mAb's pharmacokinetic and pharmacodynamics properties, and reduce drug efficacy. By reducing or removing the ADAs from circulation, the method allows for a subsequent administration of the mAb drug during the treatment to effectively treat the underlying conditions of the patient. In certain instances, the ADAs of interest may be eliminated, resulting in substantially restored activity of the mAb drug.

[0039] The IgG degrader is a molecular degrader of extracellular protein. As discussed herein, it targets pathologic circulating proteins and direct them to the liver for degradation by the endosomal/lysosomal pathway.

[0040] Preferably, the IgG degrader is a bifunctional compound having a circulating protein binding moiety (CPBM) linked to a cellular receptor binding moiety (CRBM) via a linker, wherein CPBM is an immunoglobulin G binding moiety and CRBM is an asialoglycoprotein receptor binding moiety. The term "immunoglobulin G binding moiety" or "IgGBM" is used to describe a moiety which binds to circulating IgG immunoglobulin, forming a complex with the IgG degrader. The term "asialoglycoprotein receptor binding moiety" or "ASGPBM" refers to a moiety which binds to hepatocytes through asialoglycoprotein receptors of hepatocytes. The linker is a chemical moiety having a valence from 1 to 5, or 1, 2, or 3, which covalently attaches to one or more of CRBM and/or CPBM group.

IgG DEGRADER

[0041] In an embodiment, the degrader of IgG ("IgG degrader") may have the following general chemical structure:



wherein [CPBM] is an IgG Binding Moiety which binds to pathogenic forms of IgG as identified herein, which are related to and/or mediate a disease state and/or condition and is to be removed by the action of hepatocytes or other cells on the circulating protein (the compounds preferably selectively binding to the IgG in plasma of the subject or patient);

[CRBM] is a Cellular Receptor Binding Moiety, preferably an [ASGPRBM] group, which is a binding moiety which binds to hepatocytes or other cells through asialoglycoprotein receptors or other receptors as identified herein which are on the surface of hepatocytes and other degrading cells, preferably in a patient or subject;

each [CON] is an optional connector chemical moiety which, when present, connects directly to [CPBM] or to [CRBM] or connects the [LINKER] to [CPBM] or to [CRBM] and

[LINKER] is a chemical moiety having a valency from 1 to 15 which covalently attaches to one or more [CRBM] and/or [CPBM] group, optionally through a [CON], including a [MULTICON] group, wherein said [LINKER] optionally itself contains one or more [CON] or [MULTICON] group(s);

k' is an integer from 1 to 15;

j' is an integer from 1 to 15;

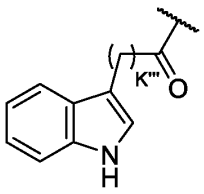
h and h' are each independently an integer from 0 to 15;

i_L is an integer from 0 to 15;

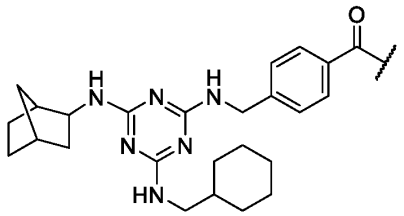
with the proviso that at least one of h, h' and i_L is at least 1, or a pharmaceutically acceptable salt, stereoisomer, solvate or polymorph thereof.

[0042] Some IgG Binding Moieties [CPBM], Cellular Receptor Binding Moieties [CRBM], and connecting group [LINKER] and [CON] are known in the art and described, for example, in International Publication No. WO 2019/199634 published October 17, 2019, and International Publication No. WO 2019/199634 published October 17, 2019, the contents of which publications are incorporated herein in their entireties by reference.

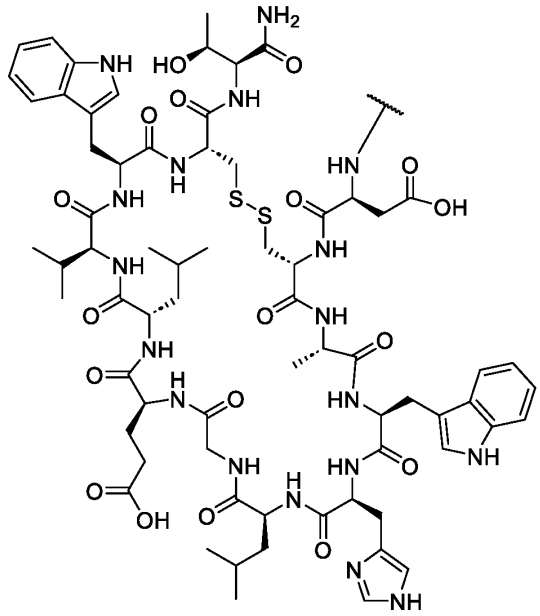
[0043] In an embodiment of the above general chemical structure, [CPBM] may be an immunoglobulin G binding moiety [IgGBM] having the structure:

i) 

;

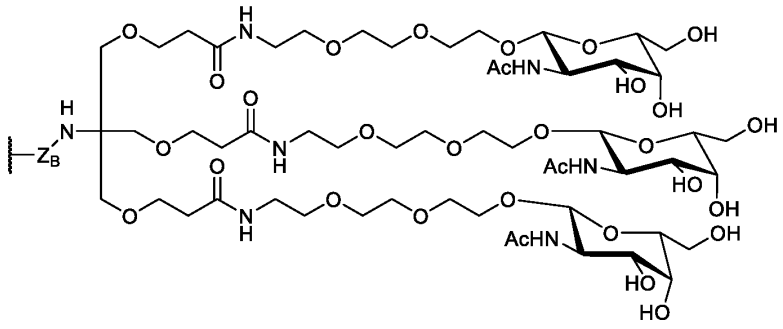
ii)  ;

iii)  ;

iv)  ; or

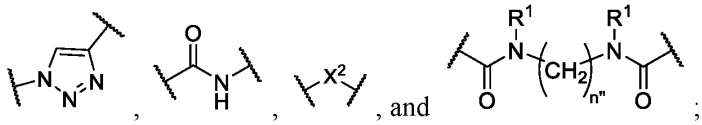
v) a peptide moiety selected from the group consisting of PAM (protein A mimetic peptide); D-PAM (D-protein A mimetic); D-PAM-Φ (phenylacetyl-D-PAM, a dendrimeric peptide ligand); TWKTSRISIF (SEQ ID NO:1); FGRLVSSIRY (SEQ ID NO:2); FcIII; FcBP-1; FcBP-2; Fc-III-4c; EPIHRSTLTALL (SEQ ID NO:3); APAR (SEQ ID NO:4); FcRM; HWRGWV (SEQ ID NO:5); HYFKFD (SEQ ID NO:6); HFRRHL (SEQ ID NO:7); HWCITGWV (SEQ ID NO:8); D2AAG; DAAG; cyclo[(N-Ac)S(A)-RWHYFK-Lact-E] (SEQ ID NO:9); cyclo[(N-Ac)–Dap(A)-RWHYFK-Lact-E] (SEQ ID NO:10); cyclo[Link-M-WFRHYK] (SEQ ID NO:11); NKFRGKYK (SEQ ID NO:12); NARKFYKG (SEQ ID NO:13); FYWHCLDE (SEQ ID NO:14); FYCHWALE (SEQ ID NO:15); FYCHTIDE (SEQ ID NO:16); RRGW (SEQ ID NO:17); and KHRFNKD (SEQ ID NO:18);

[CRBM] may be a Cellular Receptor Binding Moiety comprising N-acetyl galactosamine (GalNAc). In an embodiment, [CRBM] may have the following structure:



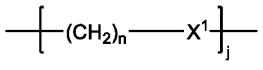
;

each [CON] may independently be at each occurrence selected from the group consisting of:



;

[LINKER] may have the structure:



;

wherein:

K''' may be 1, 2, 3, or 4;

R_M may be H or C_1-C_3 alkyl;

X^1 may be O;

each occurrence of X^2 may be independently CH_2, O, NR^4, or C(O);

each occurrence of R^1 and R^4 may be independently H or C_1-C_3 alkyl;

Z_B may be absent (a bond), -$(CH_2)_{IM}$-, -C(O)-$(CH_2)_{IM}$-, or -C(O)-$(CH_2)_{IM}$-NR_M-;

each occurrence of IM may be independently 1, 2, or 3;

k' may be 1;

each occurrence of j may be independently 1, 2, 3, 4, or 5;

j' may be 1;

h and h' may be each independently 1, 2, 3, 4, 5, 6, 7, or 8;

i_L may be 1;

each occurrence of n may be independently 2 or 3;

each occurrence of n'' may be independently 2, 3, 4, or 5;

or a salt, stereoisomer, or solvate thereof.

[0044] In another embodiment, h and h' may be each independently 1, 2, 3, 4, or 5.

[0045] In another embodiment, each occurrence of X^2 may be independently CH_2, NR^4, or C(O);

R^1 may be H; and

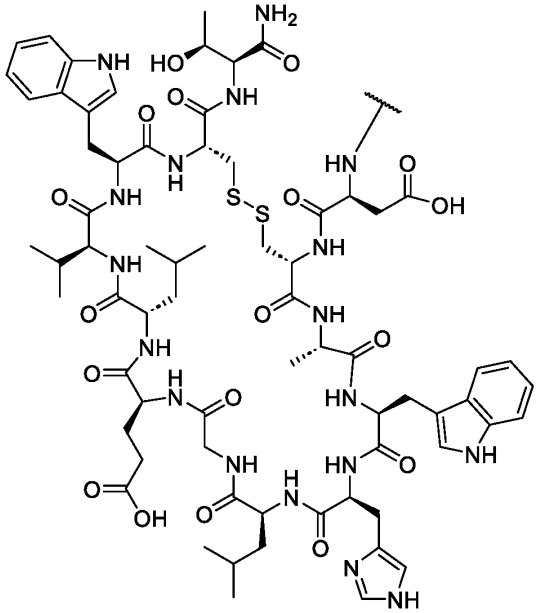
R^4 may be H.

[0046] In another embodiment, Z_B may be absent or $-C(O)-(CH_2)_{IM}-$.

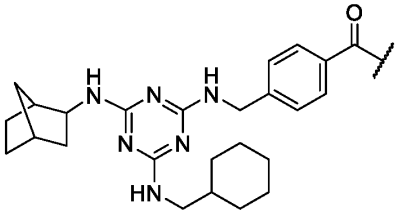
[0047] In another embodiment, the [CPBM] may be the [IgGBM] of structure:



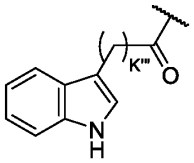
[0048] In another embodiment, the [CPBM] may be the [IgGBM] of structure:



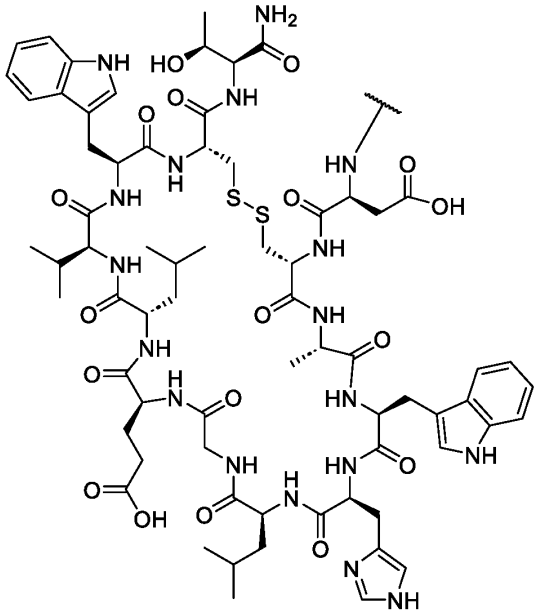
[0049] In another embodiment, the [CPBM] may be the [IgGBM] of structure:



[0050] In another embodiment, the [CPBM] may be the [IgGBM] of structure:



[0051] In another embodiment, the [CPBM] may be the [IgGBM] of structure:

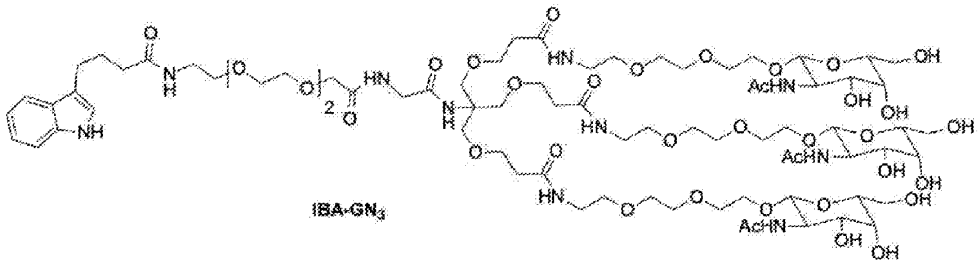


or

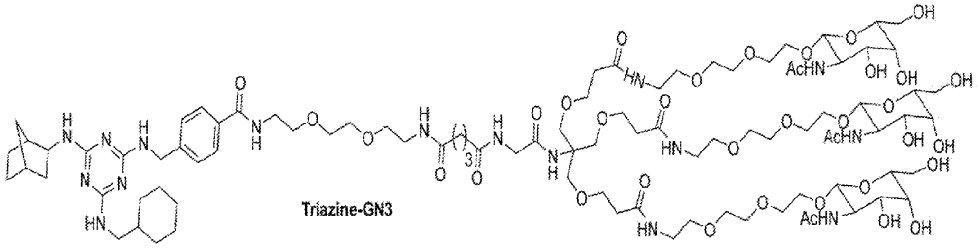


[0052] In another embodiment, [CPBM] may be an IgG binding moiety and [CRBM] may be a cellular receptor binding moiety described in International Patent Application No. PCT/US2024/026709 filed April 28, 2024, the content of which application is incorporated herein in its entirety by reference.

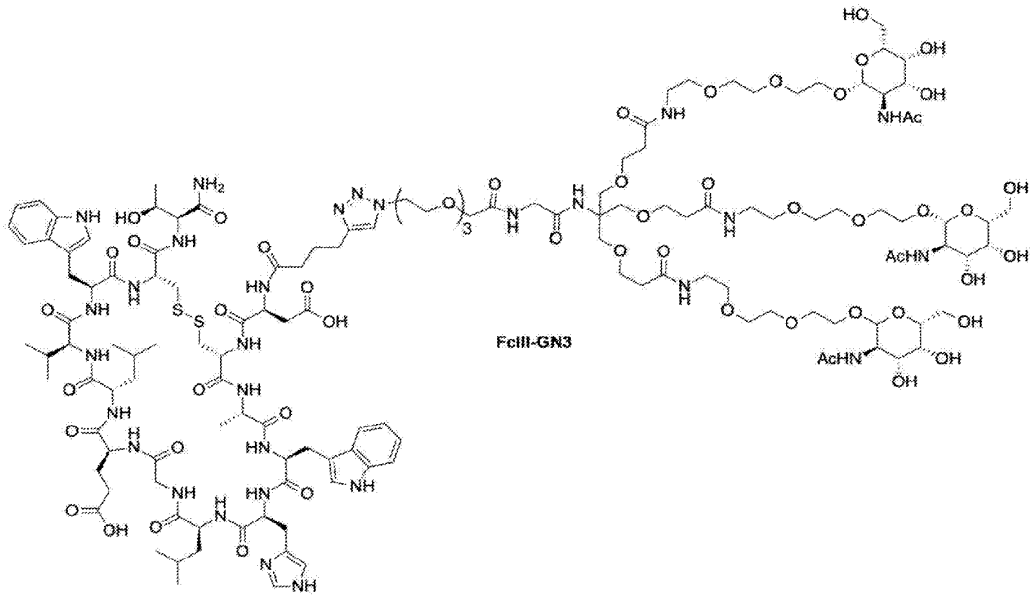
[0053] In another embodiment, the compound may have the structure:



or

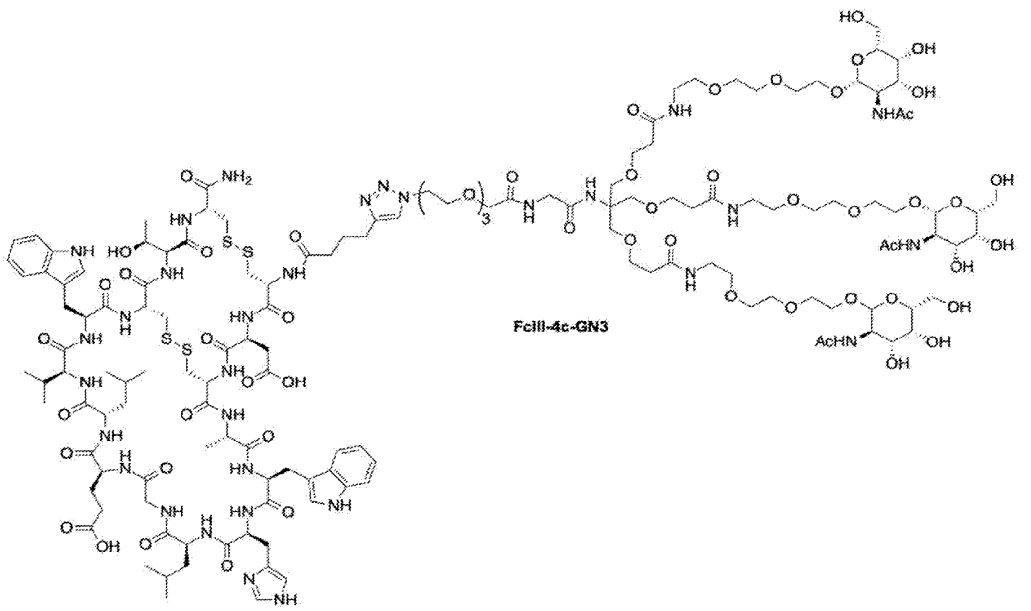


[0054] In another embodiment, the compound may have the structure:

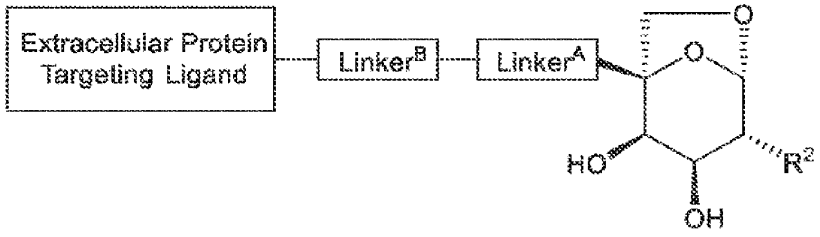


[0055] The FcIII-GN3 (FCIII-GN3) compound shows over 90% lowering of IgG in non-human primates with repeat dosing.

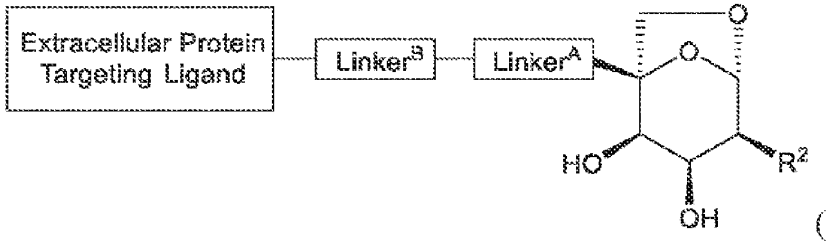
[0056] In another embodiment, the compound may have the structure:



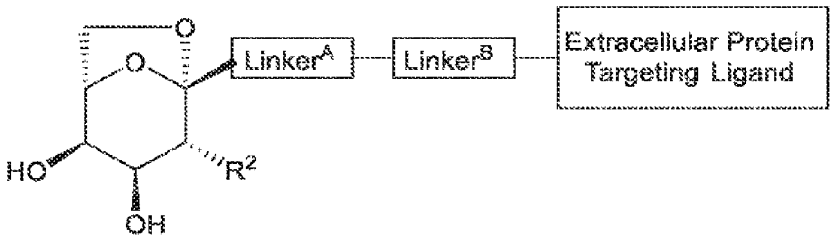
[0057] In an embodiment, the IgG degrader may have one of the following general chemical structures:



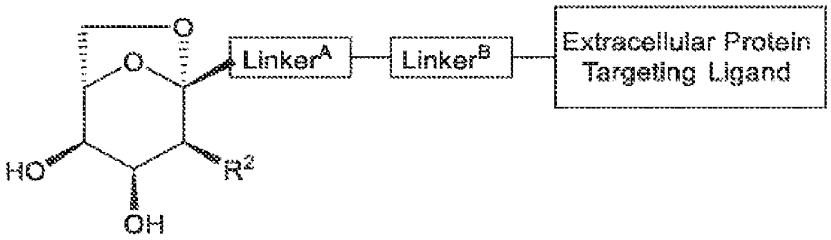
(I),



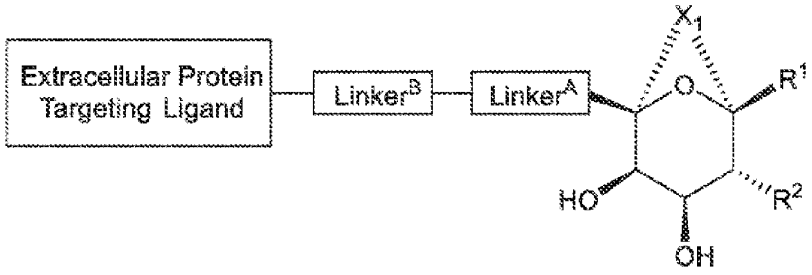
(I-d),



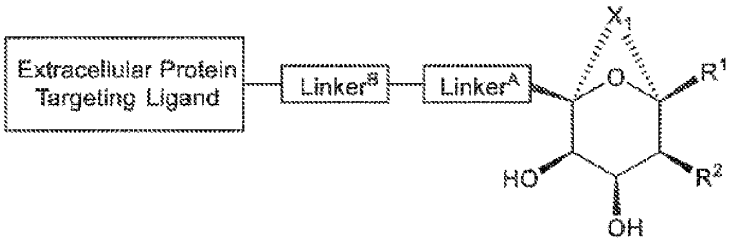
(II),



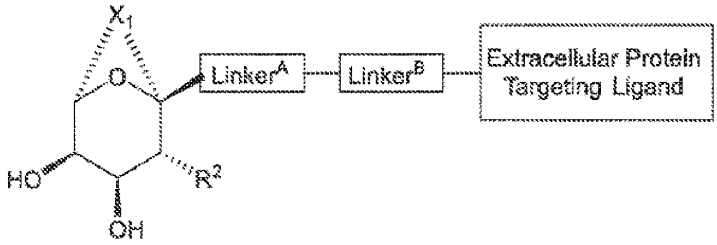
(II-d),



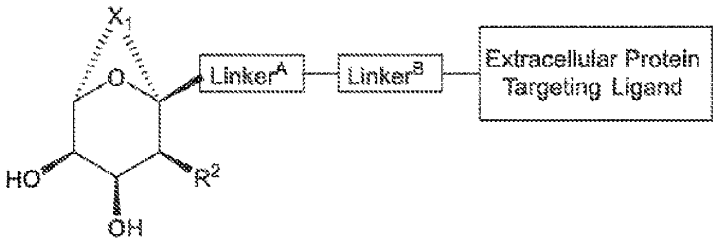
(III),



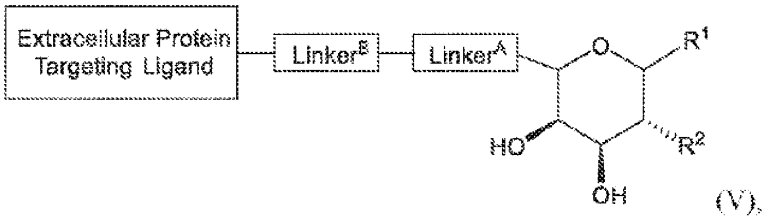
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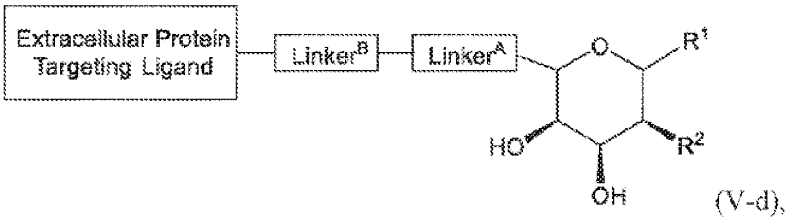
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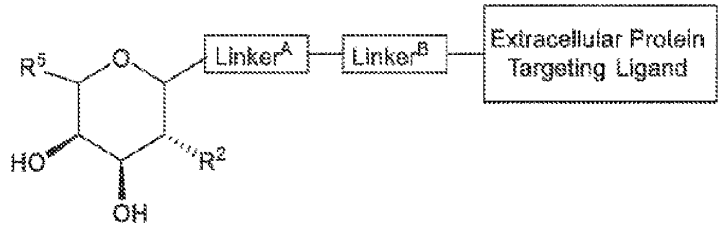
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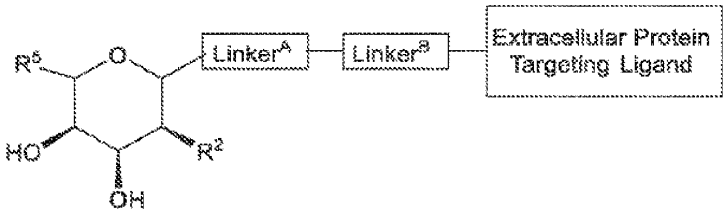
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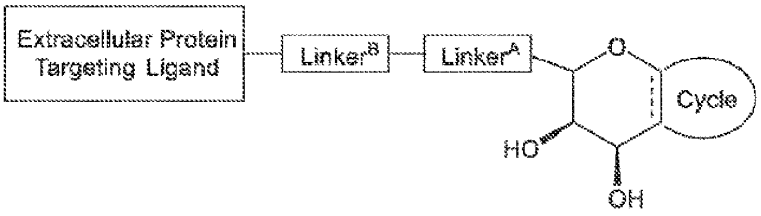
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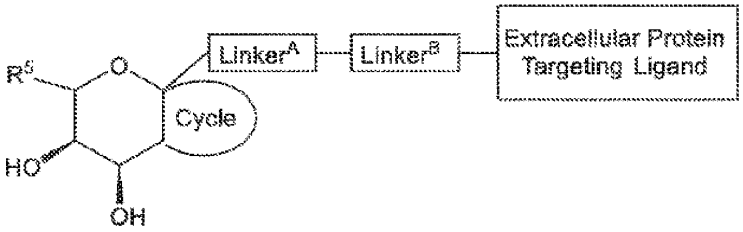
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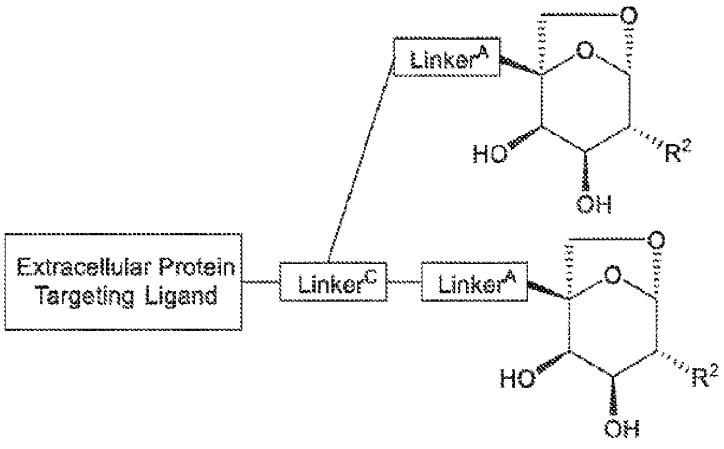
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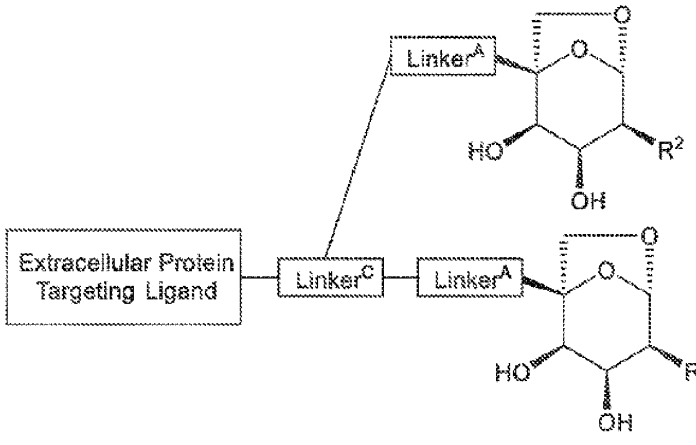
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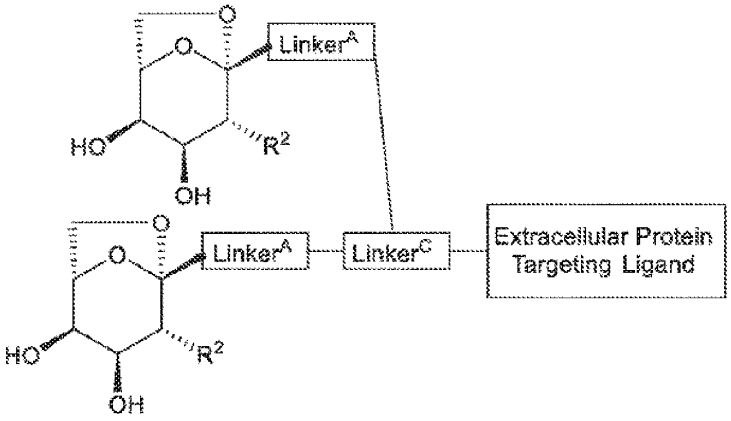
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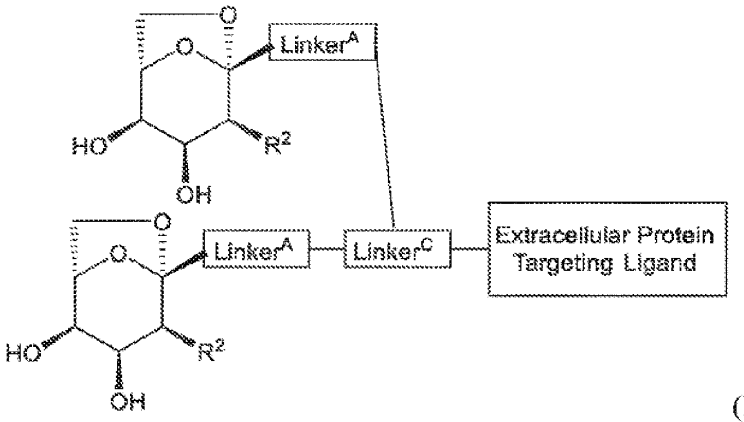
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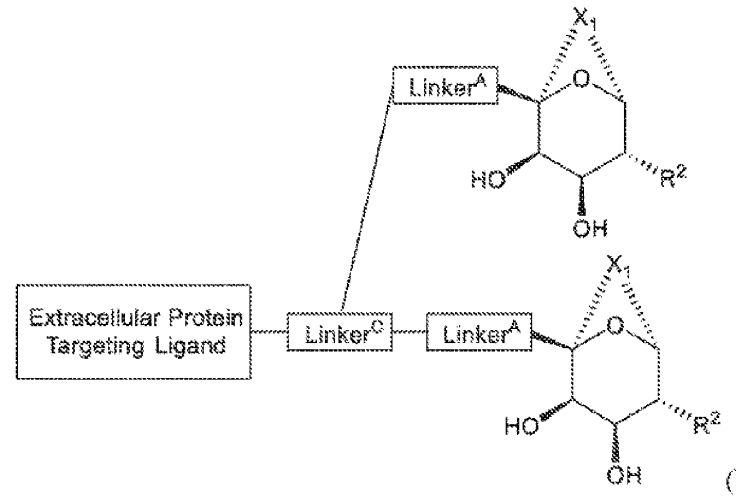
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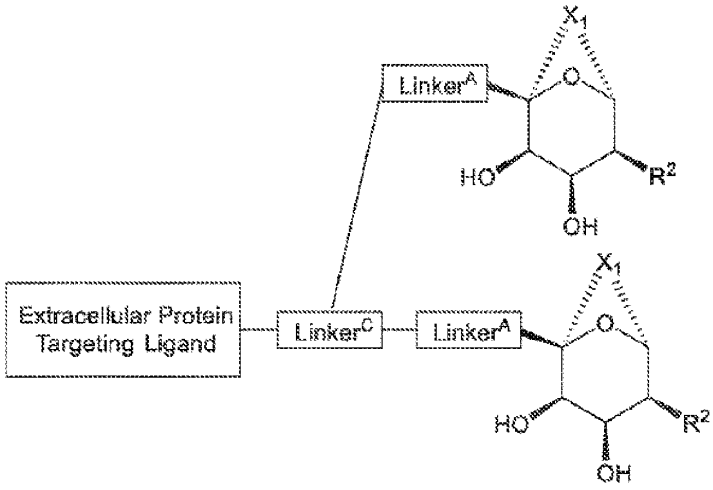
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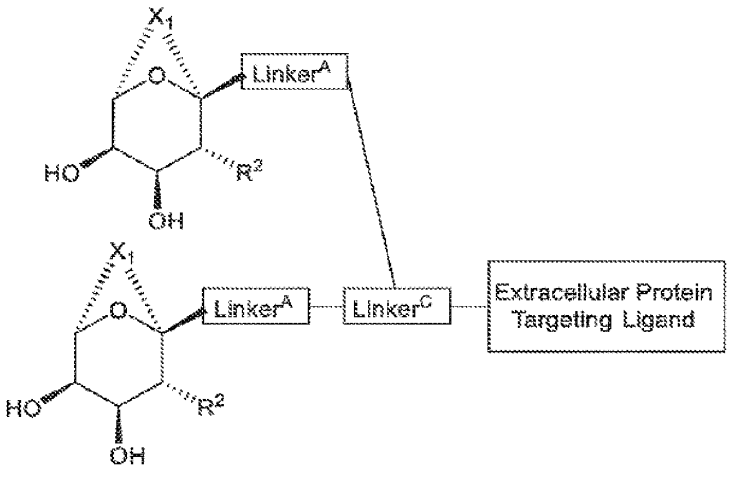
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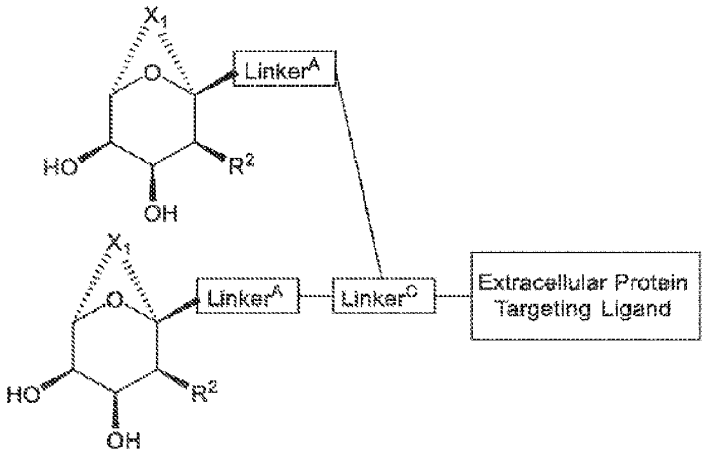
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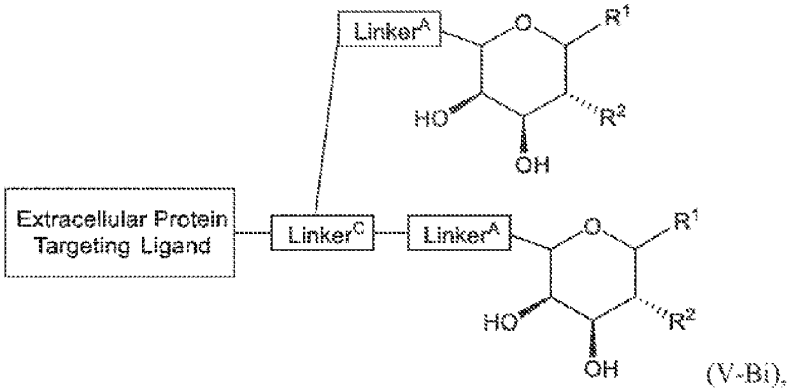
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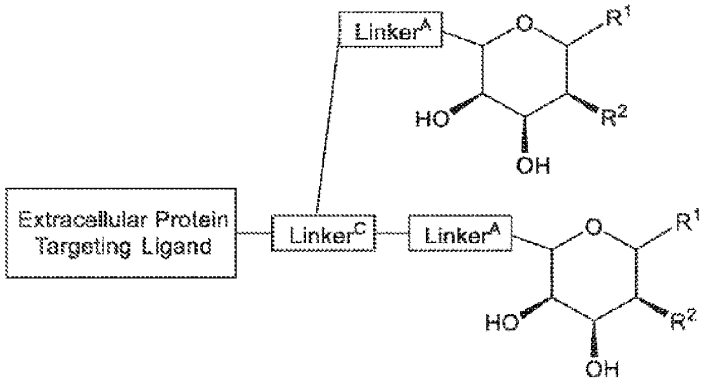
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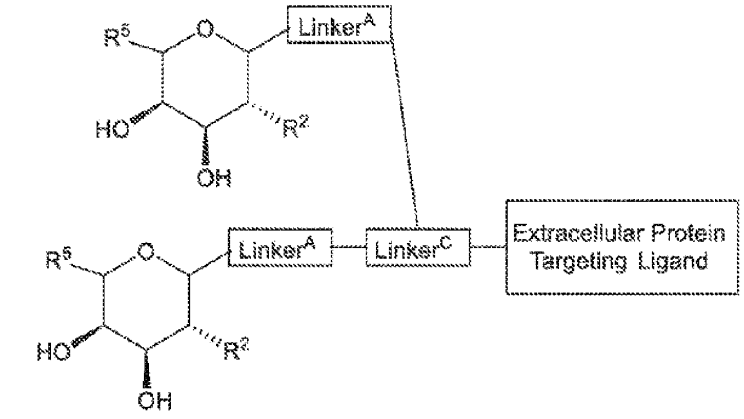
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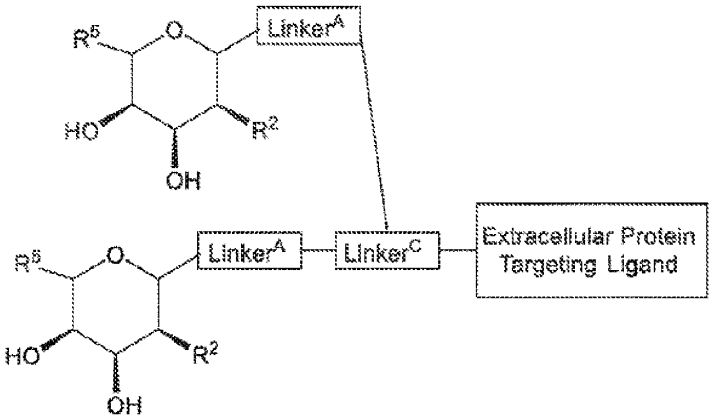
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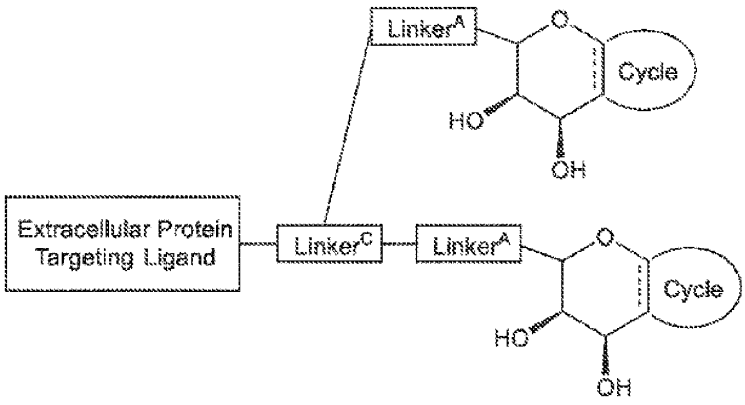
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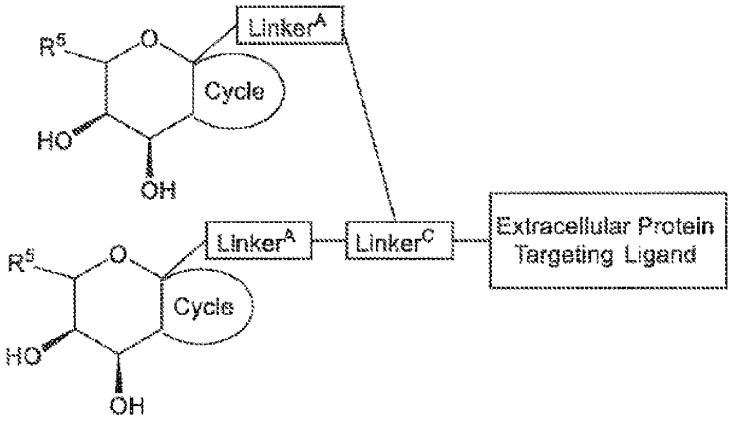
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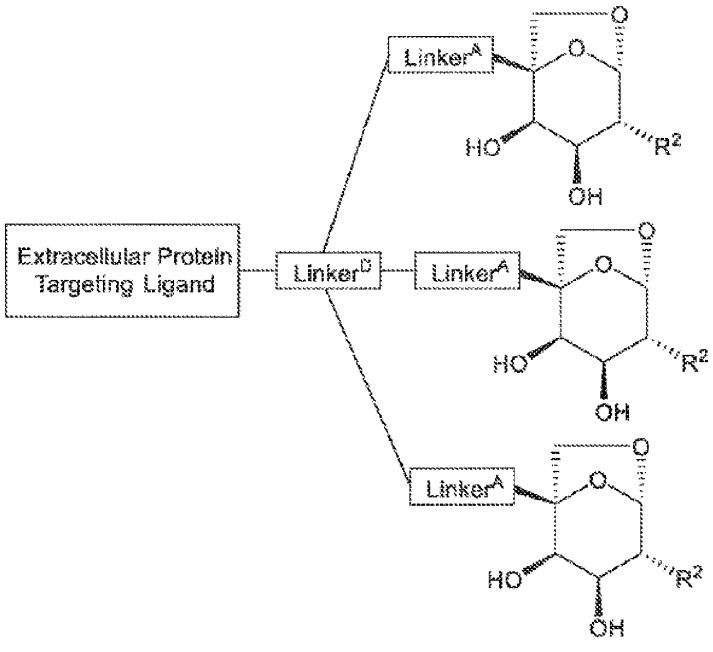
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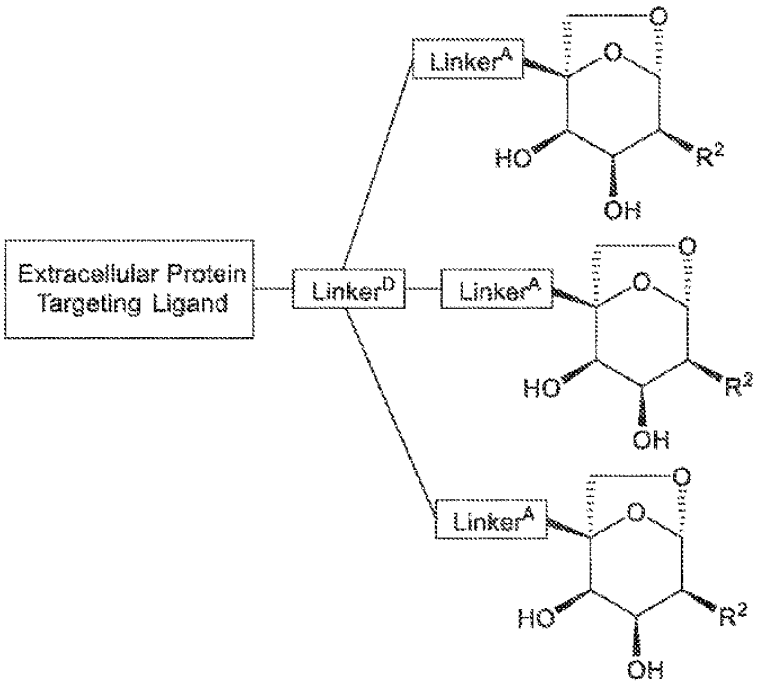
(VII-Bi),


R5
O
Cycle
HO
OH
Linker^A
Linker^A
Linker^C
Extracellular Protein Targeting Ligand
R5
O
Cycle
HO
OH

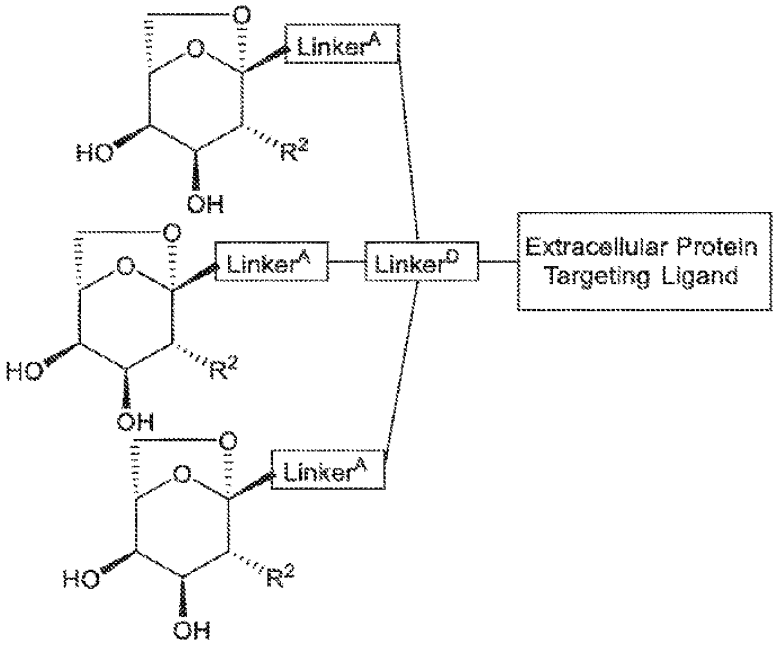
(VIII-Bi),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
O
O
HO
R2
OH
O
O
HO
R2
OH
O
O
HO
R2
OH

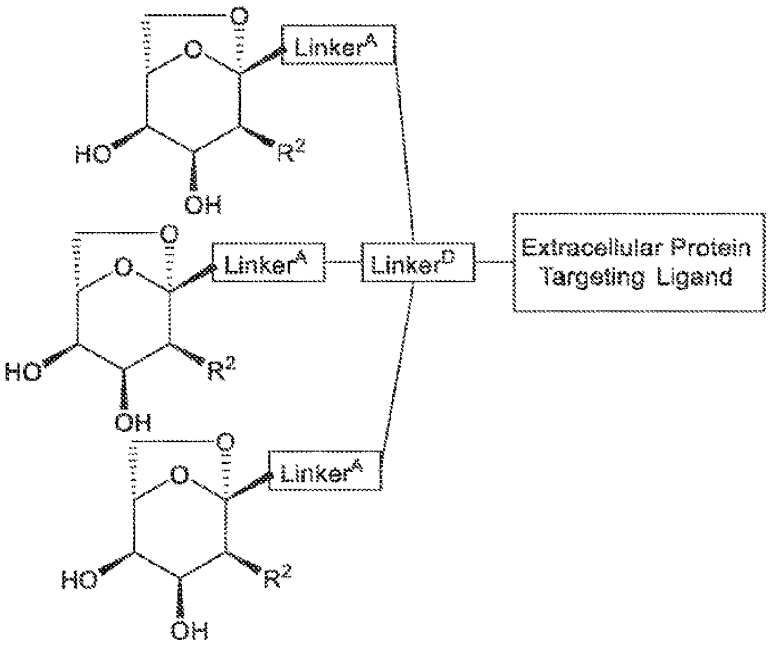
(I-Tri),


Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
Linker^A
HO
R^2
OH
O

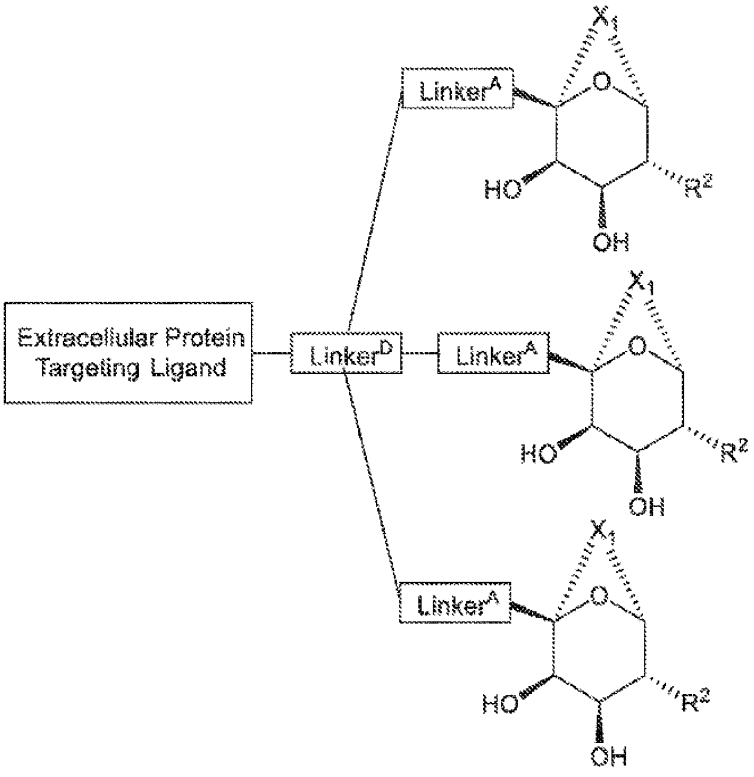
(I-d-Tri),


Linker^A
Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
HO
R^2
OH
O

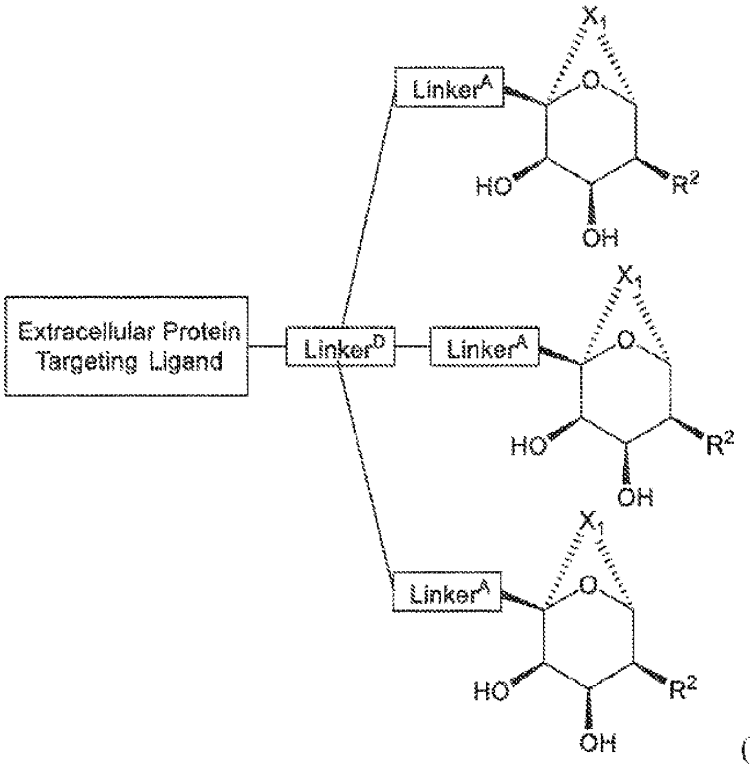
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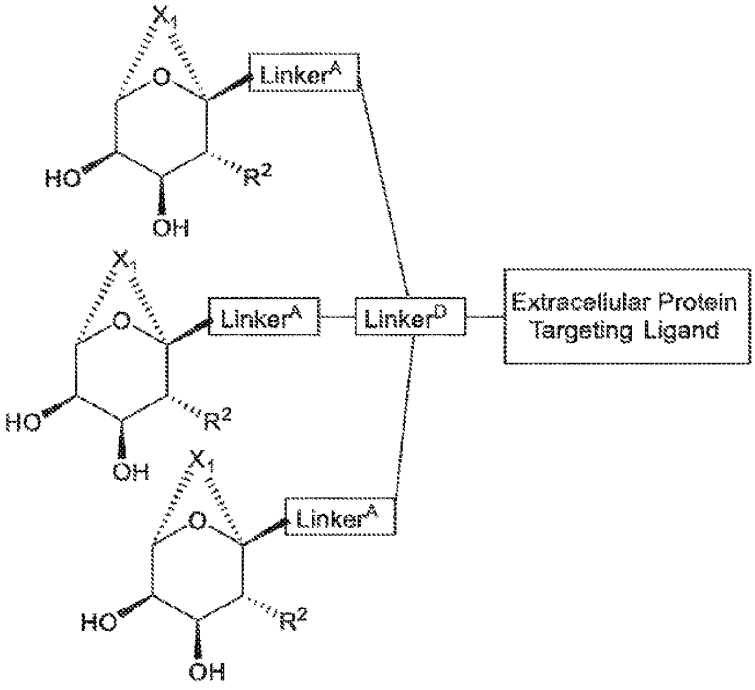
(II-d-Tri),



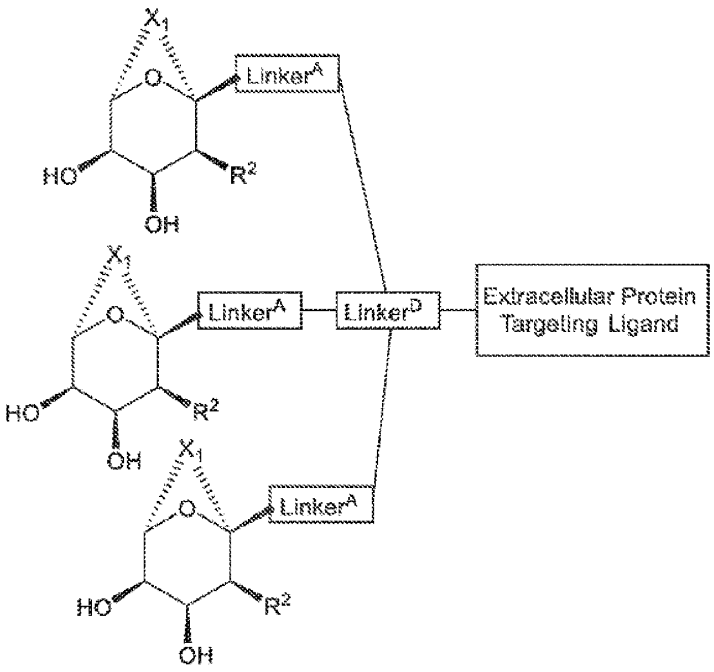
(III-Tri),



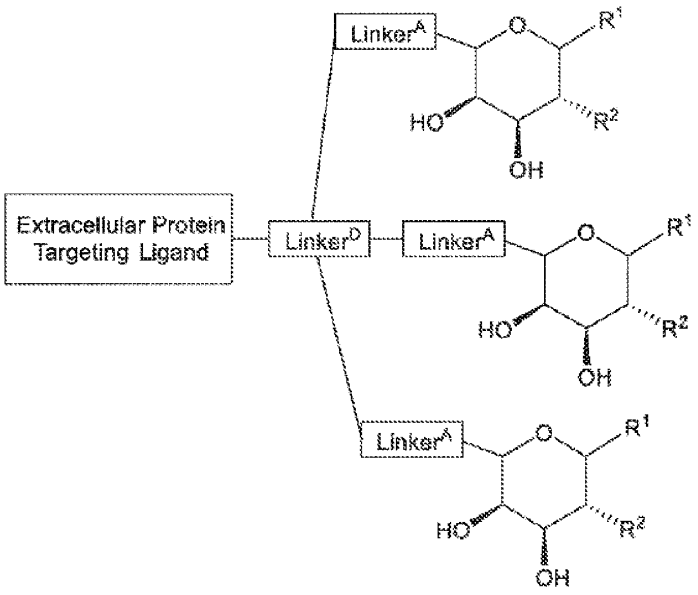
(III-d-Tri),



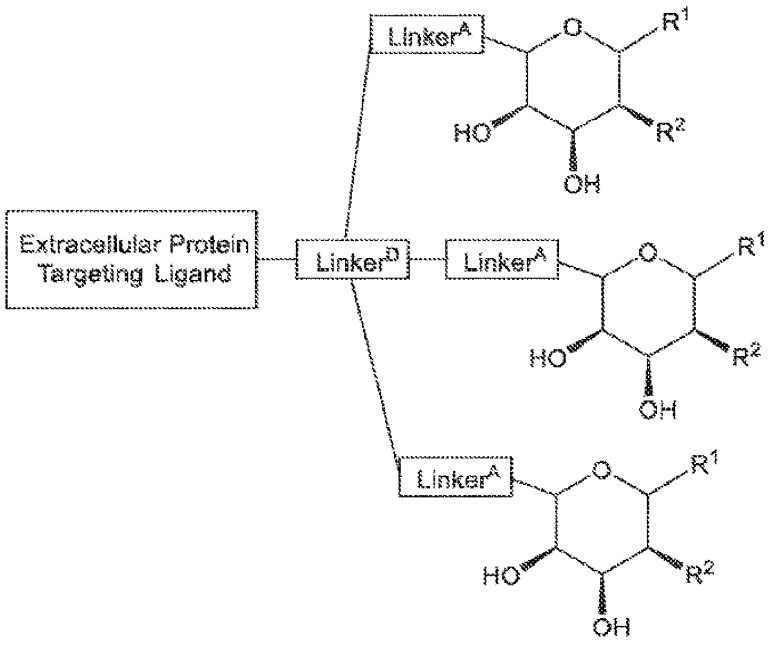
(IV-Tri),


X1
O
Linker^A
HO
R2
OH
Linker^D
Extracellular Protein Targeting Ligand

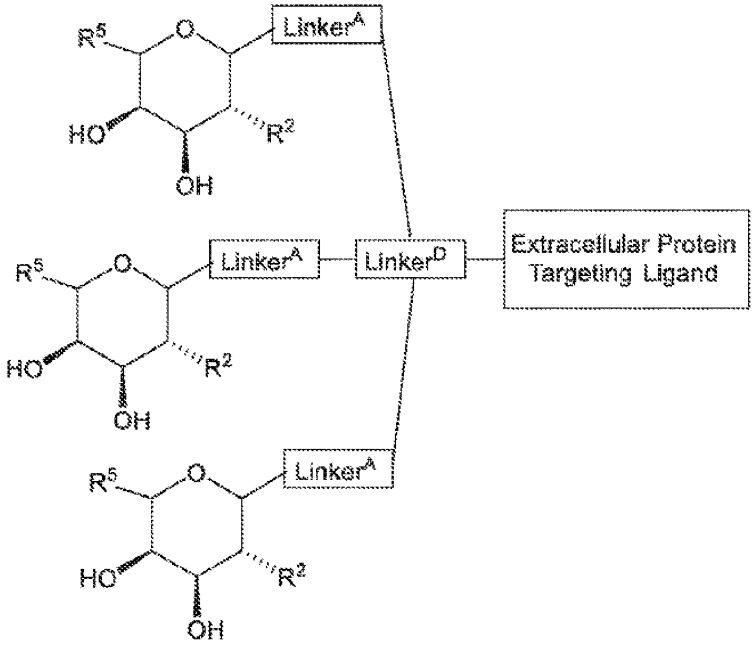
(IV-d-Tri),


Linker^A
O
R1
HO
R2
OH
Extracellular Protein Targeting Ligand
Linker^D
Linker^A

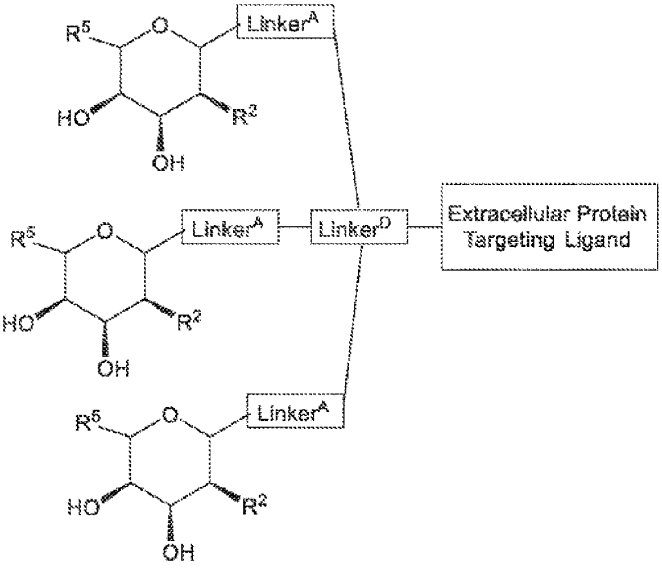
(V-Tri),


Linker^A
Extracellular Protein Targeting Ligand
Linker^D
Linker^A
Linker^A
HO
OH
O
R1
R2

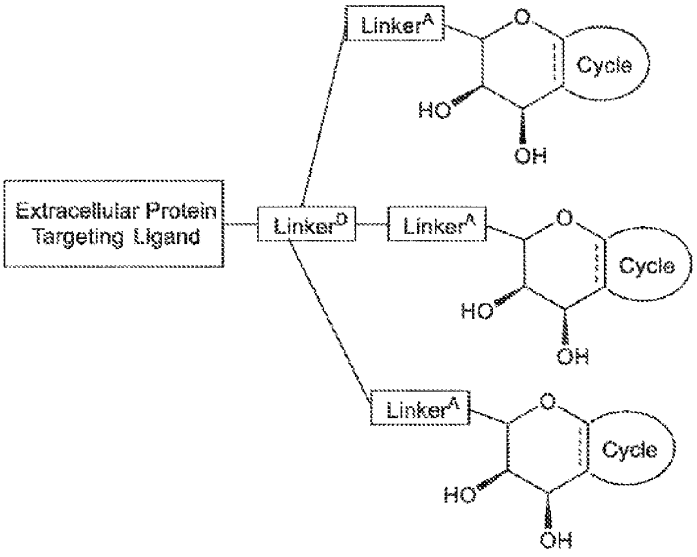
(V-d-Tri),


Linker^A
Linker^A
Linker^D
Extracellular Protein Targeting Ligand
Linker^A
R5
HO
OH
O
R2

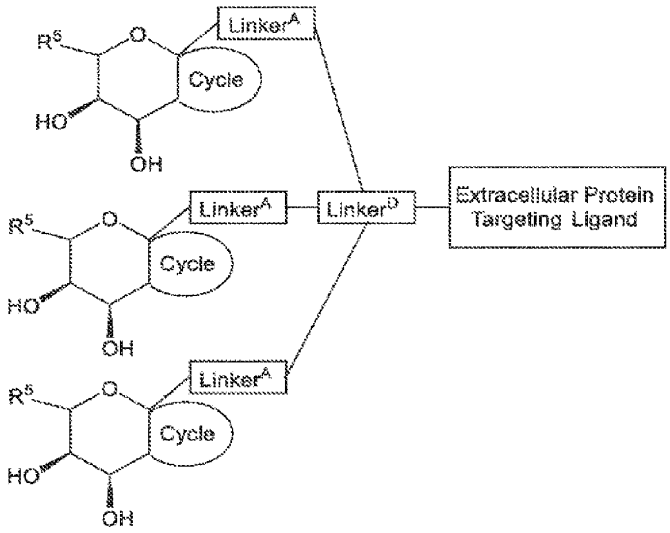
(VI-Tri),



(VI-d-Tri),



(VII-Tri), or



(VIII-Tri),

or a pharmaceutically acceptable salt thereof

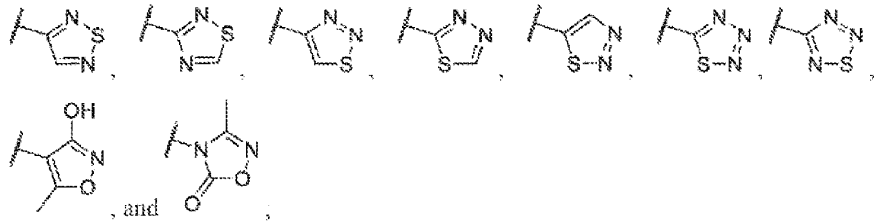
[0058] In the above formulae, "Extracellular Protein Targeting Ligand" refers to an IgG Binding Moiety [CPBM] or [IgGBM] which binds to pathogenic forms of IgG as identified herein, which are related to and/or mediate a disease state and/or condition and is to be removed by the action of hepatocytes or other cells on the circulating protein (the compounds preferably selectively binding to the IgG in plasma of the subject or patient).

[0059] In the above formulae,

X^1 is 1 to 5 groups independently selected from O, S, $N(R^6)$, and $C(R^4)(R^4)$, wherein if X^1 is 1 group then X^1 is O, S, $N(R^6)$, or $C(R^4)(R^4)$, if X^1 is 2 groups then no more than 1 group of X^1 is O, S, or $N(R^6)$, if X^1 is 3, 4, or 5 groups then no more than 2 groups of X^1 are O, S, or $N(R^6)$;

R^2 is selected from

(i) aryl, heterocycle, and heteroaryl containing 1 or 2 heteroatoms independently selected from N, O, and S, each of which aryl, heterocycle, and heteroaryl is optionally substituted with 1, 2, 3, or 4 substituents;

(ii) 

(iii) $-NR^8-S(O)-R^3$, $-NR^8-C(S)-R^3$, $-NR^8-S(O)(NR^6)-R^3$, $-N=S(O)(R^3)_2$, $-NR^8C(O)NR^9S(O)_2R^3$, $-NR^8-S(O)_2-R^{10}$, and $-NR^8-C(NR^6)-R^3$ each of which is optionally substituted with 1, 2, 3, or 4 substituents; and

(iv) hydrogen, R^{10}, alkyl-C(O)-R^3, -C(O)-R^3, alkyl, haloalkyl, -OC(O)R^3, and -NR^8-C(O)R^{10};

R^{10} is selected from aryl, alkyl-NR^8-C(O)-R^3, alkyl-aryl, alkyl-heteroaryl with 1, 2, or 4 heteroatoms, alkyl-cyano, alkyl-OR^6, alkyl-NR^6R^8, NR^8-NR^5-C(O)R^3, NR^8-$S(O)_2$-R^3, alkenyl, allyl, alkynyl, -NR^6-alkenyl, -O-alkenyl, -NR^6-alkynyl, -NR^6-heteroaryl, -NR^5-aryl, -O-heteroaryl, -O-aryl, and -O-alkynyl, each of which R^{10} is optionally substituted with 1, 2, 3, or 4 substituents;

R^1 and R^5 are independently selected from hydrogen, heteroalkyl, C_0-C_6alkyl-cyano, alkyl, alkenyl, alkynyl, haloalkyl, F, Cl, Br, I, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, heterocycloalkyl, haloalkoxy, -O-alkenyl, -O-alkynyl, C_0-C_6alkyl-OR^6, C_0-C_6alkyl-SR^6, C_0-C_6alkyl-NR^6R^7, C_0-C_6alkyl-C(O)R^3, C_0-C_6alkyl-S(O)R^3, C_0-C_6alkyl-C(S)R^3, C_0-C_6alkyl-$S(O)_2R^3$, C_0-C_6alkyl-$N(R^8)$-C(O)R^3, C_0-C_6alkyl-$N(R^8)$-S(O)R^3, C_0-C_6alkyl-$N(R^8)$-C(S)R^3, C_0-C_6alkyl-$N(R^8)$-$S(O)_2R^3$ C_0-C_6alkyl-O-C(O)R^3, C_0-C_6alkyl-O-S(O)R^3, C_0-C_6alkyl-O-C(S)R^3, -N=S(O)$(R^3)_2$, C_0-C_6alkylN_3, and C_0-C_6alkyl-O-$S(O)_2R^3$, each of which is optionally substituted with 1, 2, 3, or 4 substituents;

R^3 at each occurrence is independently selected from hydrogen, alkyl, heteroalkyl, haloalkyl (including -CF_3, -CHF_2, -CH_2F, -CH_2CF_3, -CH_2CH_2F, and -CF_2CF_3), arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR^8, and -NR^8R^9;

R^4 is independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, haloalkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocycle, -OR^6, -NR^6R^7, C(O)R^3, S(O)R^3, C(S)R^3, and $S(O)_2R^3$,

R^6 and R^7 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, haloalkyl, heteroaryl, heterocycle, -alkyl-OR^8, -alkyl-NR^8R^9, C(O)R^3, S(O)R^3, C(S)R^3, and $S(O)_2R^3$;

R^8 and R^9 are independently selected at each occurrence from hydrogen, heteroalkyl, alkyl, arylalkyl, heteroarylalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocycle;

Cycle is a 3-8 membered fused cyclic group optionally substituted with 1, 2, 3, or 4 substituents,

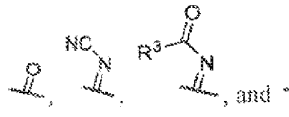
each $Linker^A$ is a bond or a moiety that covalently links the ASGPR ligand to $Linker^B$;

$Linker^B$ is a bond or a moiety that covalently links $Linker^A$ to an Extracellular Protein Targeting Ligand:

Linker^C is a chemical group that links each Linker^A to the Extracellular Protein Targeting Ligand; and

Linker^D is a chemical group that links each Linker^A to the Extracellular Protein Targeting Ligand; and

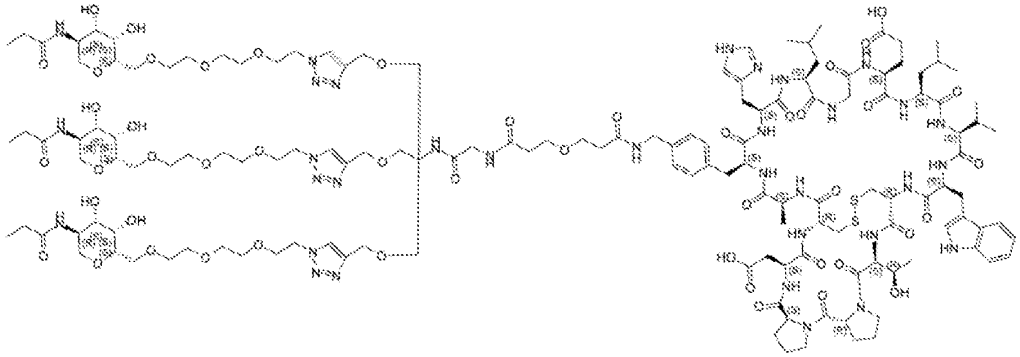
wherein, when R^2 is NR^6-alkenyl, -NR^6-alkynyl,-NR^8-C(O)R^{10}, -NR^8-$S(O)_2$-alkenyl, -NR^8-$S(O)_2$-alkynyl, -NR^6-heteroaryl, or -NR^6-aryl, then Extracellular Protein Targeting Ligand does not comprise an oligonucleotide; and

the optional substituents are selected from alkyl, alkenyl, alkynyl, haloalkyl, -OR^6, F, Cl, Br, I, -NR^6R^7, heteroalkyl, cyano, nitro, C(O)R^3, , and , as allowed by valence such that a stable compound results.

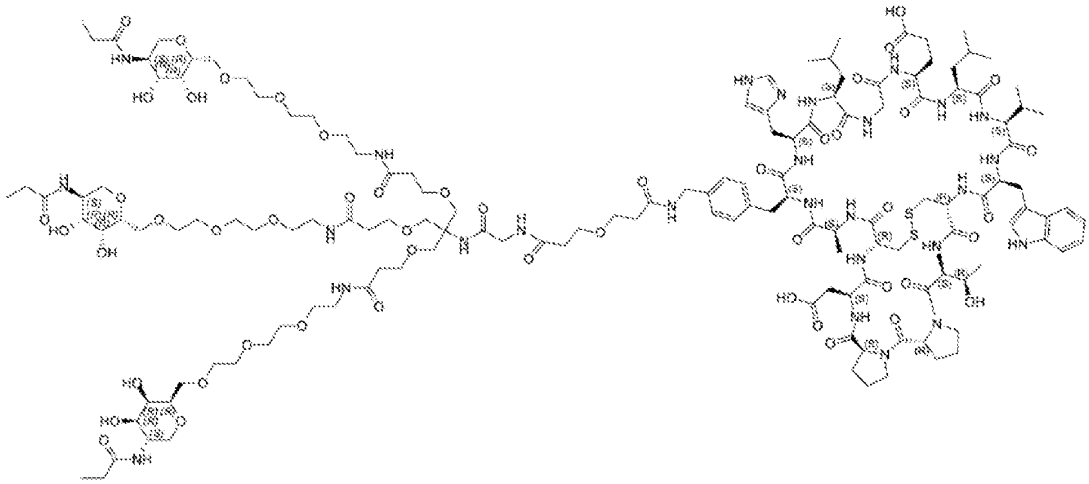
[0060] Several moieties [Linker^A], [Linker^B], [Linker^C], [LinkeD^C], [Cycle], and X^1 are known in the art and described, for example, in International Publication No. WO 2021/155317 published August 5, 2021, and International Publication No. WO 2022/235699 published November 10, 2022, the contents of which publications are incorporated herein in their entireties by reference.

[0061] In another embodiment, the compound may be a compound described in International Publication No. WO 2024/227119 published October 31, 2024, the content of which application is incorporated herein in its entirety by reference.

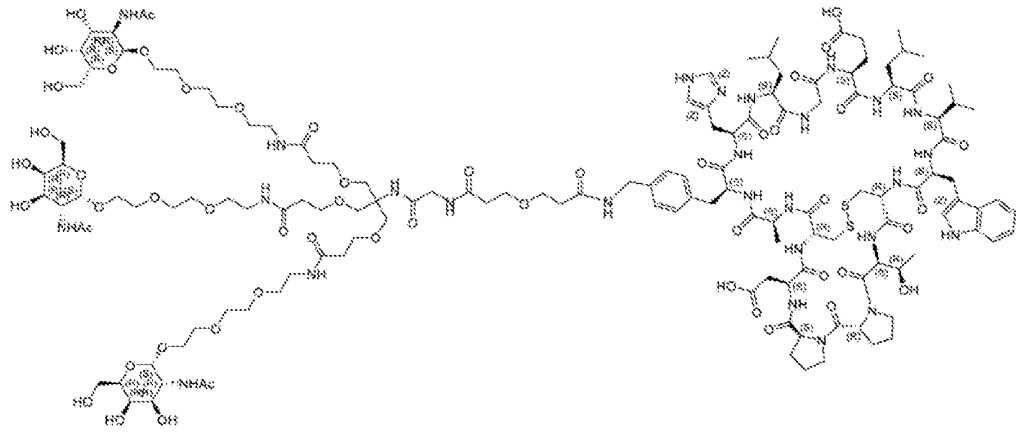
[0062] In another embodiment, the compound may have the structure:



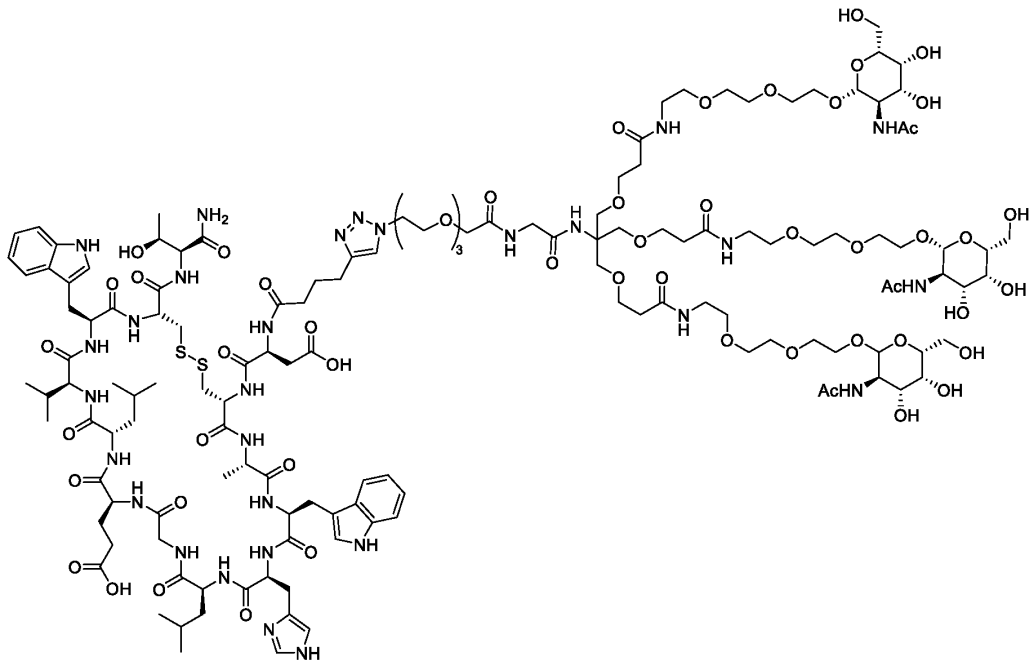
[0063] In another embodiment, the compound may have the structure:



[0064] In another embodiment, the compound may have the structure:



[0065] An example of the IgG degrader is Compound 1 having a structure represented by Formula I, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof:



Compound 1 (Formula I).

MONOCLONAL ANTIBODY DRUG

[0066] A monoclonal antibody drug (mAb) refers to an antibody produced in vitro from a single type of immune cell. A monoclonal antibody drug specifically targets and binds to a particular molecule or antigen. The mAb that is administered with the IgG degrader can be a Fn-containing biologic. As used herein, "Fc" stands for "fragment crystallizable" and refers to the region of the antibody that interacts with cell surface receptors. Examples of the Fn-containing biologic that can be administered with the IgG degrader as described herein can include adalimumab, ravulizumab, eculizumab, inebilizumab, ocrelizumab, ofatumumab, rituximab, satralizumab, tocilizumab, or a combination thereof. In some embodiments, the mAb drug can be a biological disease-modifying antirheumatic drug (dDMARD) that are produced using recombinant DNA techniques, targeting specific molecules involved in inflammation and joint destruction. Adalimumab is specifically mentioned. In some embodiments, the mAb that is administered with the IgG degrader is an IgG1-containing biologic, an IgG2-containing biologic, an IgG4-containing biologic, or a combination thereof.

[0067] Preferably, the IgG degrader is administered to the patient prior to the administration of the mAb drug during the combination treatment. The IgG degrader can be administered to the patient 4 to 50 hours, 6 to 48 hours, 10 to 48 hours, 12 to 48 hours, or 12 to 24 hours,

prior to the administration of the mAb drug during the combination treatment. Advantageously, the IgG degrader and the mAb drug can be administered to the patient on the same day during the combination treatment. Such administration would be problematic with FcRn inhibitors, as FcRn inhibitors bind to mAb, and mAb can be administered only after FcRn inhibitors are cleared from circulation, which may take a few weeks.

[0068] A preferred dose of the IgG degrader can be in the range from about 1 milligram (mg) to 300 mg, 5 mg to 250 mg, or 10 mg to 125 mg per kilogram body weight of the recipient/patient per day. A preferred dose of the mAb drug can be in the range from 10 nanogram (ng) to 300 mg, preferably 0.1 mg to 100 mg, more generally 0.5 mg to 25 mg per kilogram body weight of the recipient/patient per day.

[0069] The IgG degrader and the mAb drug can each independently be administered to the patient in a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the IgG degrader or the mAb drug.

[0070] Examples of the carriers are well known to those skilled in the art and can be prepared in accordance with acceptable pharmaceutical procedures, such as, for example, those described in Remington's Pharmaceutical Sciences, 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, Pa. (1985), the entire disclosure of which is incorporated by reference herein for all purposes. As used herein, "pharmaceutically acceptable" refers to a substance that is acceptable for use in pharmaceutical applications from a toxicological perspective and does not adversely interact with the active ingredient (e.g., the IgG degrader or the mAb drug). Accordingly, pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and are biologically acceptable. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions. Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as prolamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0071] The pharmaceutical composition that comprise the IgG degrader may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via

an implanted reservoir, among others. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the pharmaceutical composition that comprises the IgG degrader can be administered via a subcutaneous route. And the pharmaceutical composition that comprises the mAb drug can be administered intravenously, subcutaneously, or via infusion techniques.

[0072] Sterile injectable forms of the pharmaceutical compositions may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

[0073] The pharmaceutical compositions may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0074] Alternatively, the pharmaceutical compositions may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non- irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0075] The pharmaceutical compositions may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of

pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0076] The amount of the IgG degrader or the mAb drug in the pharmaceutical compositions can vary depending upon the host and disease treated, the particular mode of administration. Preferably, the compositions should be formulated to contain between 0.05 mg to 1.5 grams (g), from 0.1 mg to 1 g, 0.5 mg to 750 mg, more often 1 mg to 600 mg, and even more often 10 mg to 500 mg of active ingredient (IgG degrader or mAb drug), alone or in combination with at least one additional compound which may be used to treat the target disease or condition.

[0077] The amount of IgG degrader used in the methods of treatment of the instant invention that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the particular mode of administration. For example, the pharmaceutical composition that comprises the IgG degrader could be formulated so that a therapeutically effective dose of between 1 mg/kg and 300 mg/kg, 5 mg/kg to 250 mg/kg, or 10 mg/kg to 125 mg/kg of patient/day of the IgG degrader can be administered to a patient receiving the composition. The pharmaceutical composition that comprises the mAb drug can be formulated so that so that a therapeutically effective dose of between 10 ng/kg to 300 mg/kg, preferably 0.1 mg/kg to 100 mg/kg, or more generally 0.5 mg/kg to 25 mg/kg of patient/day of the mAb drug can be administered to a patient receiving the composition.

[0078] The IgG and mAb drug can be useful for the treatment of a disease or condition in a patient in need thereof. The diseases which may be treated in accordance with the present invention include any diseases in which the administration of IgG degrader and the mAb drug may have a therapeutic or sub- therapeutic effect. Preferably, the disease or condition may be an autoimmune disease, an inflammatory disease, cancer, or a combination thereof. For example, the disease or condition can include rheumatoid arthritis (RA), ankylosing spondylitis, psoriasis, juvenile idiopathic arthritis, non-radiographic axial spondyloarthritis, uveitis, psoriatic arthritis, Crohn's disease, systemic lupus erythematosus (SEE), Alzheimer's disease, atherosclerosis, heart disease, stroke, cancer (including leukemia), or a combination thereof. In some embodiments, a patient suffering from an autoimmune disease, an inflammatory disease or cancer can be treated by administering to the patient (subject) an effective amount of an IgG degrader and an mAb drug according to the present invention optionally in pharmaceutically acceptable carriers or diluents, and optionally in combination with other known pharmaceutical agents, preferably agents which can assist in treating

autoimmune and/or inflammatory diseases or cancer, or ameliorating the secondary effects and/or symptoms associated with these diseases or conditions. This treatment can also be administered in conjunction with other conventional therapies, such as radiation treatment or surgery for cancer. The selection of the additional agents to be administered in combination with the IgG degrader and the mAb drug are dependent, among other things, on the disease being treated, the selection of which can be made by one of ordinary skill in the art, e.g., a physician.

[0079] In some embodiments, the patient can be a human being who has been exposed to the mAb drug prior to the combination treatment and experienced a reduced efficacy of the mAb drug, a side effect such as increased drug clearance, adverse immune reactions or infusion-related reactions, or a combination thereof due to the formation of the ADAs induced by the mAb drug.

[0080] As discussed herein, the IgG degrader can restore mAb's therapeutic activity through ADA removal. Thus, a method of restoring a therapeutic activity of a monoclonal antibody drug in a patient comprises: administering to the patient a therapeutically effective amount of an IgG degrader, wherein the IgG degrader is effective to bind to an ADA induced by the mAb.

[0081] In one aspect, the invention also provides kits for use in the instant methods. Kits can include at least two containers where one container includes the IgG degrader, and the other container includes the mAb drug as described herein and instructions for use in accordance with any of the method described herein. Generally, these instructions comprise a description of administration of the IgG degrader, the mAb drug to treat, ameliorate or prevent a disease or condition, e.g., an autoimmune disease, an inflammatory disease, or cancer, according to any of the method described herein. The kit may, for example, comprise a description of selecting an individual suitable for treatment based on identifying whether that individual has ADAs generated in response to the administration of the mAb drug due to a prior treatment. The instructions are typically provided in the form of a package insert, or label, in accordance with the requirements of the regulatory having authority over the jurisdiction where the pharmaceutical composition is to be provided to patients.

[0082] The invention is further illustrated by the following non-limiting examples.

EXAMPLES

IgG degrader

[0083] The IgG degrader used in the examples is Compound 1 having a structure represented by Formula 1. Preparation of Compound 1 has been described in WO 2019/199634 (FcIII-GN3), the content of which is incorporated herein by reference in its entirety.

Example 1

[0084] A non-human primate (NHP) study was conducted to evaluate the effect of single and multiple doses of Compound 1 on IgG reduction.

[0085] FIG. 1 shows the IgG lowering results after administering a single dose of Compound 1 to NHPs at different dosing levels, and is a plot of IgG percentage relative to baseline over time after start of infusion of Compound 1 in NHPs. As shown in FIG. 1, a single dose of Compound 1 can lead to 80% IgG reduction in two to three days. This contrasts with FcRn inhibitors such as efgartigimod, which typically requires five to seven days of dosing to reach 50% IgG reduction. (Ulrichts P et al., J Clin Invest, 2018 Oct 1; 128 (10):4372-4386. doi: 10.1172/JCI97911. Epub 2018 Jul 24. PMID: 30040076; PMCID: PMC6159959) Accordingly, Compound 1 IgG inhibitor can achieve more rapid and deeper IgG lowering than FcRn inhibitors.

[0086] FIG. 2 shows multiple dose administration results and is a plot of IgG percentage relative to baseline over time after start of infusion of Compound 1 in Cyno monkey. The figure shows that the depth of IgG lowering can reach 90% after second dose of Compound 1 IgG degrader. The results indicate that the depth of lowering is tunable and can be easily adjusted by frequency of administration. Accordingly, multiple dose administration of the IgG inhibitor can be specifically tailored to treat both acute and chronic disease indications.

Example 2

[0087] A study was conducted to evaluate the safety of Compound 1 IgG degrader in healthy humans. IgG1, IgG2, IgG3, and IgG4 values (µmol per liter [µmol/L]) from absolute change and percent of baseline are shown in Tables 2-5 respectively.

[0088] The IgG degrader demonstrates a clean safety profile, with no serious adverse events and no clinically significant laboratory abnormalities.

Table 2. IgG1 values (µmol/L) from absolute change and percent of baseline –safety analysis set

Variable Time Since Dose	IgG degrader 50 mg N=6	IgG degrader 125 mg	Pooled Placebo N=4

	n	Mean	(SD)	N=6 n	Mean	(SD)	n	Mean	(SD)
Absolute Value (µmol/L)									
Baseline	6	45.7	(12.42)	6	37.7	(7.15)	4	37.4	(5.93)
Day 1 4 hours	6	41.6	(12.43)	6	32.0	(8.65)	3	38.2	(3.11)
Day 2 24 hours	6	45.7	(11.40)	5	37.0	(7.89)	3	39.0	(10.98)
Day 3 48 hours	6	48.7	(14.24)	1	40.8	(NE)	4	38.8	(5.08)
Day 4 72 hours	6	45.8	(11.17)				2	46.2	(13.49)
Day 5 96 hours	6	46.6	(10.94)				2	32.9	(5.24)
Day 8	6	45.1	(14.30)				2	33.1	(5.94)
Day 15	6	28.3	(6.76)				2	39.1	(6.56)
Day 22	6	42.6	(9.28)				2	36.4	(4.29)
Change from Baseline (µmol/L)									
Day 1 4 hours	6	-4.1	(10.88)	6	-5.7	(5.24)	3	2.7	(7.92)
Day 2 24 hours	6	-0.1	(3.74)	5	0.5	(1.13)	3	2.4	(12.48)
Day 3 48 hours	6	2.9	(5.65)	1	2.8	(NE)	4	1.4	(9.16)
Day 4 72 hours	6	0.1	(6.34)				2	12.8	(19.20)
Day 5 96 hours	6	0.9	(4.46)				2	-0.4	(0.47)
Day 8	6	-0.6	(3.49)				2	-0.2	(11.65)
Day 15	6	-17.4	(14.65)				2	5.7	(12.26)
Day 22	6	-3.1	(7.09)				2	3.1	(10.00)
Percent of Baseline (%)									
Day 1 4 hours	6	92.4	(18.33)	6	85.4	(13.85)	3	110.2	(26.16)
Day 2 24 hours	6	101.1	(12.10)	5	101.3	(2.79)	3	109.4	(38.38)
Day 3 48 hours	6	107.1	(16.33)	1	107.4	(NE)	4	106.7	(29.09)
Day 4 72 hours	6	102.5	(18.71)				2	144.1	(65.17)
Day 5 96 hours	6	103.5	(12.01)				2	98.9	(1.23)
Day 8	6	98.0	(8.55)				2	102.5	(35.40)
Day 15	6	66.2	(24.05)				2	120.7	(40.35)
Day 22	6	95.8	(18.26)				2	112.0	(32.06)

Table 3. IgG2 values (µmol/L) from absolute change and percent of baseline - safety analysis set

Variable Time Since Dose	IgG degrader 50 mg N=6 n	Mean	(SD)	IgG degrader 125 mg N=6 n	Mean	(SD)	Pooled Placebo N=4 n	Mean	(SD)
Absolute Value (µmol/L)									
Baseline	6	21.4	(7.25)	6	27.7	(5.30)	4	28.1	(2.35)
Day 1 4 hours	6	19.6	(7.38)	6	24.1	(7.26)	3	29.8	(4.57)
Day 2 24 hours	6	22.0	(6.17)	5	28.4	(7.51)	3	27.8	(8.81)
Day 3 48 hours	6	22.5	(6.56)	1	26.2	(NE)	4	29.1	(7.31)
Day 4 72 hours	6	23.5	(8.81)				2	27.6	(1.79)

Day 5	96 hours	6	22.4	(7.22)			2	29.7	(5.19)
Day 8		6	21.0	(6.71)			2	28.4	(10.94)
Day 15		6	13.9	(6.70)			2	31.9	(9.34)
Day 22		6	20.5	(6.31)			2	30.1	(8.21)
Change from Baseline (µmol/L)									
Day 1	4 hours	6	-1.8	(3.86)	6	-3.7	(3.69)	3	0.8	(4.13)
Day 2	24 hours	6	0.6	(2.70)	5	0.2	(1.71)	3	0.6	(8.22)
Day 3	48 hours	6	1.1	(3.08)	1	1.3	(NE)	4	1.0	(5.71)
Day 4	72 hours	6	2.1	(4.83)				2	-0.4	(0.71)
Day 5	96 hours	6	1.0	(2.62)				2	1.6	(4.10)
Day 8		6	-0.4	(2.63)				2	0.4	(9.86)
Day 15		6	-7.5	(6.61)				2	3.8	(8.25)
Day 22		6	-0.9	(3.27)				2	2.0	(7.12)
Percent of Baseline (%)									
Day 1	4 hours	6	92.6	(15.81)	6	85.8	(15.01)	3	102.7	(14.42)
Day 2	24 hours	6	106.0	(17.67)	5	99.9	(5.92)	3	102.0	(29.58)
Day 3	48 hours	6	108.0	(18.93)	1	105.1	(NE)	4	102.6	(20.32)
Day 4	72 hours	6	111.2	(22.58)				2	98.4	(2.58)
Day 5	96 hours	6	106.5	(15.45)				2	105.5	(14.42)
Day 8		6	99.7	(13.53)				2	100.6	(35.12)
Day 15		6	66.1	(24.20)				2	113.1	(28.92)
Day 22		6	98.2	(22.94)				2	106.8	(25.13)

Table 4. IgG3 values (µmol/L) from absolute change and percent of baseline – safety analysis set

Variable Time Since Dose	IgG degrader 50 mg N=6 n Mean (SD)	IgG degrader 125 mg N=6 n Mean (SD)	Pooled Placebo N=4 n Mean (SD)
Absolute Value (µmol/L)			
Baseline	6 4.3 (1.35)	6 4.4 (0.89)	4 4.1 (2.73)
Day 1 4 hours	6 4.1 (1.40)	6 3.9 (0.76)	3 2.8 (0.15)
Day 2 24 hours	6 4.4 (1.13)	5 4.5 (0.75)	3 4.7 (3.66)
Day 3 48 hours	6 4.4 (0.86)	1 4.5 (NE)	4 3.9 (1.78)
Day 4 72 hours	6 4.2 (1.05)		2 3.2 (0.15)
Day 5 96 hours	6 4.4 (1.16)		2 2.8 (0.46)
Day 8	6 4.0 (0.96)		2 2.4 (0.18)
Day 15	6 3.1 (1.86)		2 2.9 (0.17)
Day 22	6 4.0 (1.05)		2 2.8 (0.24)
Change from Baseline (µmol/L)			
Day 1 4 hours	6 -0.1 (0.45)	6 -0.5 (0.70)	3 0.0 (0.29)
Day 2 24 hours	6 0.1 (0.38)	5 0.3 (0.13)	3 0.2 (0.69)
Day 3 48 hours	6 0.1 (0.52)	1 0.4 (NE)	4 -0.3 (1.02)

Day 4	72 hours	6	-0.0	(0.51)			2	0.5	(0.69)
Day 5	96 hours	6	0.1	(0.33)			2	0.1	(0.08)
Day 8		6	-0.3	(0.51)			2	-0.4	(0.37)
Day 15		6	-1.2	(0.88)			2	0.2	(0.37)
Day 22		6	-0.3	(0.64)			2	0.1	(0.31)
Percent of Baseline (%)									
Day 1	4 hours	6	96.9	(12.41)	6	89.2	(14.10)	3	102.5	(11.04)
Day 2	24 hours	6	105.5	(10.66)	5	108.1	(3.26)	3	102.8	(18.51)
Day 3	48 hours	6	105.7	(13.67)	1	109.6	(NE)	4	101.5	(20.94)
Day 4	72 hours	6	101.4	(14.82)				2	122.3	(30.04)
Day 5	96 hours	6	103.6	(9.56)				2	102.6	(3.65)
Day 8		6	96.3	(10.81)				2	88.1	(11.15)
Day 15		6	68.8	(23.14)				2	109.1	(15.55)
Day 22		6	96.6	(16.75)				2	104.5	(12.21)

Table 5. IgG4 values (µmol/L) from absolute change and percent of baseline – safety analysis set

Variable Time Since Dose	IgG degrader 50 mg N=6 n Mean (SD)			IgG degrader 125 mg N=6 n Mean (SD)			Pooled Placebo N=4 n Mean (SD)		
Absolute Value (µmol/L)									
Baseline	6	3.0	(2.18)	6	3.8	(2.53)	4	2.5	(2.28)
Day 1 4 hours	6	3.0	(2.09)	6	3.3	(2.15)	3	3.2	(1.99)
Day 2 24 hours	6	3.2	(2.20)	5	4.2	(2.75)	3	1.5	(0.98)
Day 3 48 hours	6	3.3	(2.27)	1	1.9	(NE)	4	2.6	(2.38)
Day 4 72 hours	6	2.8	(2.09)				2	3.5	(1.66)
Day 5 96 hours	6	3.2	(2.10)				2	2.0	(0.35)
Day 8	6	3.1	(2.13)				2	1.8	(0.04)
Day 15	6	1.7	(0.85)				2	2.2	(0.12)
Day 22	6	2.8	(1.69)				2	2.1	(0.88)
Change from Baseline (µmol/L)									
Day 1 4 hours	6	-0.0	(0.54)	6	-0.5	(0.47)	3	-0.0	(0.30)
Day 2 24 hours	6	0.2	(0.35)	5	0.1	(0.21)	3	0.0	(0.37)
Day 3 48 hours	6	0.2	(0.36)	1	0.2	(NE)	4	0.1	(0.35)
Day 4 72 hours	6	-0.2	(1.02)				2	1.5	(2.04)
Day 5 96 hours	6	0.1	(0.45)				2	0.0	(0.04)
Day 8	6	0.0	(0.30)				2	-0.2	(0.43)
Day 15	6	-1.3	(1.43)				2	0.2	(0.50)
Day 22	6	-0.2	(0.76)				2	0.1	(0.31)
Percent of Baseline (%)									
Day 1 4 hours	6	100.7	(17.74)	6	86.6	(11.91)	3	102.5	(14.54)
Day 2 24 hours	6	106.7	(17.13)	5	100.2	(5.45)	3	103.4	(19.10)

Day 3	48 hours	6	107.4	(17.80)	1	108.9	(NE)	4	95.1	(29.24)
Day 4	72 hours	6	95.2	(29.76)				2	183.0	(116.93)
Day 5	96 hours	6	104.9	(15.06)				2	100.5	(1.97)
Day 8		6	100.2	(14.44)				2	91.1	(19.54)
Day 15		6	72.7	(28.54)				2	111.7	(27.21)
Day 22		6	96.8	(20.54)				2	104.2	(16.20)

Example 3

[0089] Cell based internalization experiments were carried out to characterize the effects of Compound 1 IgG degrader on Fc-containing biologics. One day before the testing, cells were cultured in the presence of perylene diimide (PDI) on a plate. Anti-adalimumab antibody and Compound 1 were then added. Internalization was carried out for 24 hours. Fluorescence was measured, and the results are illustrated in FIG. 3.

[0090] FIG. 3 shows the fluorescence data of anti-adalimumab antibody internalization. The results indicate that Compound 1 IgG degrader binds and degrades anti-adalimumab antibody in vitro.

Example 4

[0091] A study was conducted in non-naïve NHPs to evaluate the effect of Compound 1 IgG degrader on the concentration of adalimumab when adalimumab is administered with the IgG degrader. The tested subjects received single doses of adalimumab (3 mg/kg SC x1) at various times relative to the IgG degrader (30 mg/kg IV x1). The concentration of adalimumab was determined by ELISA (enzyme-linked immunosorbent assay).

[0092] FIG. 4 shows that the IgG degrader has no effect on adalimumab PK when administered 12 hours after the degrader. The results indicate that IgG degrader such as Compound 1 is compatible with biologic therapeutics when dosed 12 hours prior, and can be administered with biologics with little effect on PK.

Example 5

[0093] A study was conducted to evaluate the ability of the IgG degrader to remove adalimumab ADAs and restore anti-TNFα activity. The study design is illustrated in FIG. 6. Cyno monkeys received adalimumab (10 mg/kg) in complete Freund's adjuvant (CFA) followed by two once weekly (QW) doses of adalimumab in phosphate buffered saline (PBS) (10 mg/kg). ADA positive cyno monkeys were randomized to Groups 1 and 2, and ADA negative cyno monkeys were placed in Group 3. Group 2 received active drug (Compound 1

IgG degrader 50 mg/kg IV x1) while Groups 1 and 3 received placebo. After 24 hours, all cyno monkeys received adalimumab (3 mg/kg SC x1). Readouts included adalimumab PK, adalimumab's neutralizing activity of TNFα, total IgG and PK of Compound 1 IgG degrader.

[0094] FIG. 5 shows that ADAs induced by administration of adalimumab are reduced greater than 80% at 48 hours with a single dose of Compound 1 IgG degrader.

[0095] FIG. 6 shows that there were significant improvements in adalimumab anti-TNFα activity in Compound 1 IgG degrader treated ADA+ cyno monkeys vs. PBO (Group 2 Compound 1 degrader vs. Group 1 Vehicle).

[0096] Conclusion: These data demonstrate an IgG degrader (e.g., Compound 1) does not adversely affect exposure to adalimumab and that it can reduce neutralizing ADAs. The IgG degrader can be administered with bDMARDs. Thus, the IgG degrader offers a unique combinatorial therapeutic approach for difficult to treat diseases or conditions (e.g., RA) and other rheumatologic diseases, enabling removal of ADAs, pathogenic autoantibodies, and immune complexes as key differentiated features compared to other approaches.

Example 6

[0097] BHV-1300 was used to assess the elimination of anti-Humira antibody Adalimumab, an antibody that has been shown to exhibit neutralizing effects of Humira binding to TNFα. To measure ASGPR1 mediated endocytosis of Adalimumab via BHV-1300, Adalimumab was labeled with Alexa-Fluor 647 using non-specific lysine conjugation to conjugate a fluorescent dye to the antibody. Adalimumab-647 was added to HEK293-ASGPR1 expressing cells at 6 nM concentration. BHV-1300 was then added to the cells as a 7 point dose-curve starting at a high concentration of 250 nM with 3-fold dilution steps. A no compound vehicle control was also included. The assay plate was incubated at 37 ºC and 5% CO_2 in the Incucyte instrument, collecting 3 phase and near-IR (NIR) images per well for 48 hours post BHV-1300 dosing. Incucyte analysis software was used to process individual images and subtract background fluorescent signal. A dose response-curve was visualized in the NIR channel to demonstrate BHV-1300 mediated endocytosis of Adalimumab.

[0098] To assess the functional effect of removing a neutralizing antibody, a 2 step experiment was performed to first demonstrate a dose-dependent endocytosis of Adalimumab by BHV-1300 and second to demonstrate that removal of the antibody results in a reversal of the neutralizing effect of Humira binding to TNFα. On day 1, HEK-293 ASGPR1 cells were incubated with 6 nM Adalimumab-647 and 18 nM biotinylated TNFα pre-incubated with 4.5

nM streptavidin-488. A no compound vehicle control or 7-point curve of BHV-1300 starting at a high concentration of 250 nM with 3-fold dilution steps was added to the cells. The assay plate was incubated at 37 ºC in the Incucyte instrument, collecting near-IR and green images for 24 hours. At 24 hours after the addition of BHV-1300, cells exhibited a dose-response curve in the NIR channel demonstrating endocytosis of Adalimumab-647 via BHV-1300. There was no signal in the green channel from no endocytosis of TNFα. Immediately following the imaging of the 24-hour time point, a constant 0.5 nM Humira and 10 nM BHV-1300 was added to all wells to utilize Humira endocytosis via BHV-1300 as a readout for Adalimumab neutralization activity. The assay plate was incubated at 37 ºC in the Incucyte instrument, collecting near-IR and green images for an additional 24 hours. In wells that received no compound on day 1, no green signal is observed upon Humira internalization as a result of the neutralizing effects of Adalimumab preventing Humira binding to TNFα-488. A dose-response curve in the green channel is observed 24 hours after the addition of Humira for wells treated with BHV-1300 on day 1, suggesting that BHV-1300 mediated removal of the neutralizing anti-Humira antibody Adalimumab restores the binding of Humira to TNFα.

[0099] Set forth below are various aspects of the disclosure.

[0100] Aspect 1. A method of treating a disease or a condition in a patient in need thereof, the method comprising administering to the patient an immunoglobulin G degrader and a monoclonal antibody drug (also referred to as “combination treatment”), wherein the immunoglobulin G degrader is effective to bind to an anti-drug antibody induced by the monoclonal antibody drug.

[0101] Aspect 2. The method of aspect 1, wherein the immunoglobulin G degrader is administered to the patient prior to the administration of the monoclonal antibody drug during the treatment (or combination treatment).

[0102] Aspect 3. The method of aspect 1 or aspect 2, wherein the patient has been previously treated with the monoclonal antibody prior to administering the immunoglobulin G degrader.

[0103] Aspect 4. The method of any one of aspects 1 to 3, wherein the immunoglobulin G degrader is administered to the patient 4 to 50 hours prior to the administration of the monoclonal antibody drug during the treatment (or combination treatment).

Aspect 5. The method of any of aspects 1 to 4, wherein the immunoglobulin G degrader and the monoclonal antibody are administered to the patient on the same day during the treatment (or combination treatment).

[0104] Aspect 6. The method of any of aspects 1 to 5, wherein the monoclonal antibody drug is a Fc-containing biologic.

[0105] Aspect 7. The method of aspect 6, wherein the Fc-containing biologic comprises adalimumab, ravulizumab, eculizumab, inebilizumab, ocrelizumab, ofatumumab, rituximab, satralizumab, tocilizumab, or a combination thereof.

[0106] Aspect 8. The method of any of aspects 1 to 7, wherein the monoclonal antibody drug is adalimumab.

[0107] Aspect 8A. The method of any of aspects 1 to 5, wherein the monoclonal antibody drug is an IgG1-containing biologic, an IgG2-containing biologic, an IgG4-containing biologic, or a combination thereof.

[0108] Aspect 9. The method of any of the preceding aspects, wherein the immunoglobulin G degrader is a bifunctional compound having a circulating protein binding moiety (CPBM) linked to a cellular receptor binding moiety (CRBM) via a linker, wherein the CPBM is an immunoglobulin G binding moiety, and the CRBM is an asialoglycoprotein receptor binding moiety.

[0109] Aspect 10. The method of any of aspects 1 to 9, wherein the immunoglobulin G degrader comprises a compound of Formula I as disclosed herein, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof.

[0110] Aspect 11. The method of any of aspects 1 to 9, wherein the immunoglobulin G degrader comprises a compound of Formula II as disclosed herein, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof.

[0111] Aspect 12. The method of any of aspects 1 to 9, wherein the immunoglobulin G degrader comprises a compound of Formula III as disclosed herein, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof.

[0112] Aspect 13. The method of any of aspects 1 to 9, wherein the immunoglobulin G degrader comprises a compound of Formula IV as disclosed herein, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof.

[0113] Aspect 14. The method of any of aspects 1 to 13, wherein the immunoglobulin G degrader is administered to the patient in a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the immunoglobulin G degrader.

[0114] Aspect 15. The method of any of aspects 1 to 14, wherein the immunoglobulin G degrader is administered subcutaneously.

[0115] Aspect 16. The method of any of aspects 1 to 15, wherein the patient has been exposed to the monoclonal antibody drug prior to the treatment and experienced a reduced efficacy of the monoclonal antibody drug, a side effect, or a combination thereof, due to the formation of the anti-drug antibody.

[0116] Aspect 17. The method of any of aspects 1 to 16, further comprising forming a binary complex between the monoclonal antibody drug and tumor necrosis factor alpha, and removing the binary complex from circulation upon the administration of the immunoglobulin G degrader.

[0117] Aspect 18. The method of aspect 17, wherein the administration of the immunoglobulin G degrader results in formation of a ternary complex between the monoclonal antibody drug, tumor necrosis factor alpha, and the immunoglobulin G degrader, and wherein the ternary complex is removed from circulation through asialoglycoprotein receptors of hepatocytes.

[0118] Aspect 19. The method of any of aspects 1 to 18, further comprising forming a binary complex between the anti-drug antibody and the monoclonal antibody drug, and removing the binary complex from circulation upon the administration of the immunoglobulin G degrader.

[0119] Aspect 20. The method of aspect 19, wherein the administration of the immunoglobulin G degrader results in formation of a ternary complex between the anti-drug antibody, the monoclonal antibody drug, and the immunoglobulin G degrader, and wherein the ternary complex is removed from circulation through asialoglycoprotein receptors of hepatocytes.

[0120] Aspect 21. The method of any of aspects 1 to 20, wherein the disease or condition is an autoimmune disease, an inflammatory disease, cancer, or a combination thereof.

[0121] Aspect 22. The method of any of the aspects 1 to 21, wherein the disease or condition is rheumatoid arthritis, ankylosing spondylitis, psoriasis, juvenile idiopathic arthritis, non-radiographic axial spondyloarthritis, uveitis, psoriatic arthritis, Crohn's disease, systemic lupus erythematosus, Alzheimer's disease, atherosclerosis, heart disease, stroke, or a combination thereof.

[0122] Aspect 23. A method of restoring a therapeutic activity of a monoclonal antibody drug in a patient, the method comprising: administering to the patient a therapeutically effective amount of an immunoglobulin G degrader, wherein the immunoglobulin G degrader is effective to bind to an anti-drug antibody induced by the monoclonal antibody drug.

[0123] Aspect 24. The method of aspect 23, further comprising testing the patient to confirm that the anti-drug antibody is present in the patient prior to the administration of the immunoglobulin G degrader.

[0124] Aspect 25. The method of aspect 23 or aspect 24, wherein the monoclonal antibody drug is a Fc-containing biologic comprising adalimumab, ravulizumab, eculizumab, inebilizumab, ocrelizumab, ofatumumab, rituximab, satralizumab, tocilizumab, or a combination thereof, and the immunoglobulin G degrader is a bifunctional compound having a circulating protein binding moiety (CPBM) linked to a cellular receptor binding moiety (CRBM) via a linker, wherein the CPBM is an immunoglobulin G binding moiety, and the CRBM is an asialoglycoprotein receptor binding moiety.

[0125] Aspect 26. The method of any of aspects 23 to 25, wherein the immunoglobulin G degrader is administered to the patient at a dose of 10 mg/kg to 200 mg/kg.

[0126] Aspect 27. A kit for treating a patient afflicted with a disease or condition in which a monoclonal antibody drug is clinically relevant, the kit including: (a) the monoclonal antibody drug; and (b) instructions for administering the monoclonal antibody with an IgG degrader by one of the methods of aspects 1 to 22.

[0127] Aspect 28. A kit for treating a patient afflicted with a disease or condition in which a monoclonal antibody drug is clinically relevant, the kit including: (a) the monoclonal antibody drug; and (b) instructions for restoring a therapeutic activity of a monoclonal antibody drug by one of the methods of aspects 23 to 26.

[0128] The composition and method can alternatively comprise, consist of, or consist essentially of, any appropriate materials or steps herein disclosed. The composition and method can additionally, or alternatively, be formulated so as to be devoid, or substantially free, of any materials (or species), or steps, which are otherwise not necessary to the achievement of the function or objectives of the composition and method.

[0129] All cited patents, patent applications, and other references are incorporated herein by reference in their entirety.

[0130] While particular embodiments have been described, alternatives, modifications, variations, improvements, and substantial equivalents that are or may be presently unforeseen may arise to applicants or others skilled in the art.

CLAIMS

What is claimed is:

1. A method of treating a disease or a condition in a patient in need thereof, the method comprising administering to the patient an immunoglobulin G degrader and a monoclonal antibody drug, wherein the immunoglobulin G degrader is effective to bind to an anti-drug antibody induced by the monoclonal antibody drug.

2. The method of claim 1, wherein the immunoglobulin G degrader is administered to the patient prior to the administration of the monoclonal antibody drug during the treatment.

3. The method of claim 1 or claim 2, wherein the patient has been previously treated with the monoclonal antibody prior to administering the immunoglobulin G degrader.

4. The method of any one of claims 1 to 3, wherein the immunoglobulin G degrader is administered to the patient 4 to 50 hours prior to the administration of the monoclonal antibody drug during the treatment.

5. The method of any of claims 1 to 4, wherein the immunoglobulin G degrader and the monoclonal antibody are administered to the patient on the same day during the treatment.

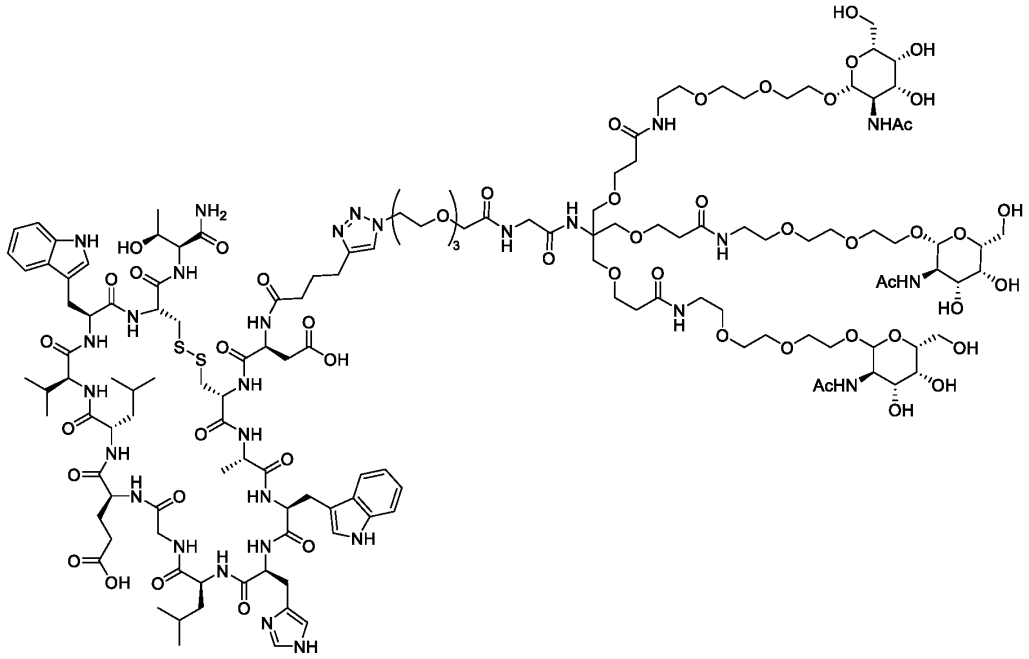
6. The method of any of claims 1 to 5, wherein the monoclonal antibody drug is a Fc-containing biologic.

7. The method of claim 6, wherein the Fc-containing biologic comprises adalimumab, ravulizumab, eculizumab, inebilizumab, ocrelizumab, ofatumumab, rituximab, satralizumab, tocilizumab, or a combination thereof.

8. The method of any of claims 1 to 7, wherein the monoclonal antibody drug is adalimumab.

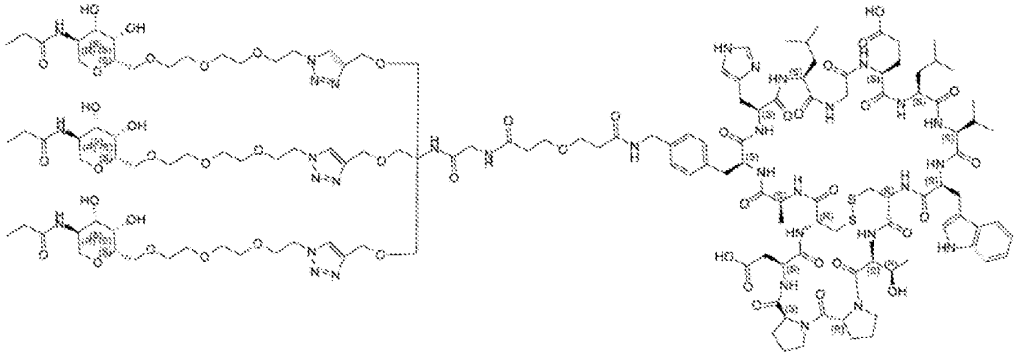
9. The method of any of claims 1 to 8, wherein the immunoglobulin G degrader is a bifunctional compound having a circulating protein binding moiety (CPBM) linked to a cellular receptor binding moiety (CRBM) via a linker, wherein the CPBM is an immunoglobulin G binding moiety, and the CRBM is an asialoglycoprotein receptor binding moiety.

10. The method of any of claims 1 to 9, wherein the immunoglobulin G degrader comprises a compound of Formula I, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof:



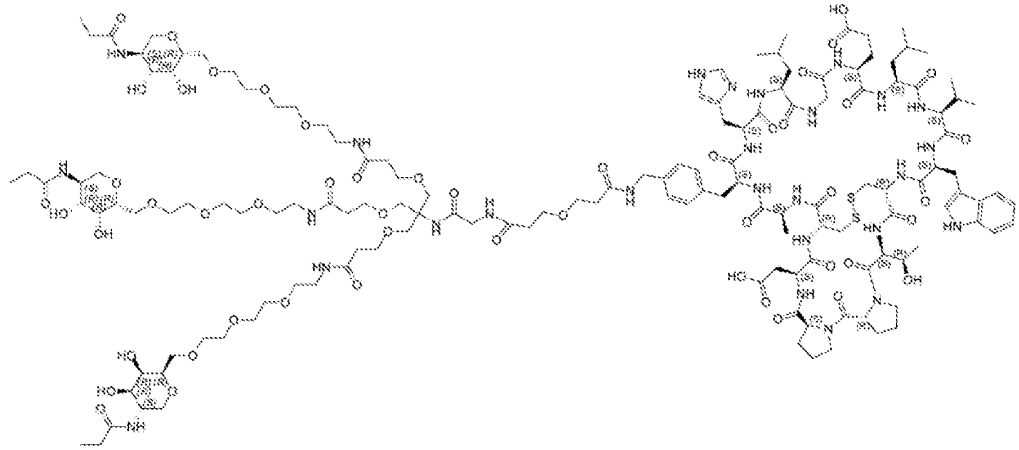
Formula I.

11. The method of any of claims 1 to 9, wherein the immunoglobulin G degrader comprises a compound of Formula II, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof:



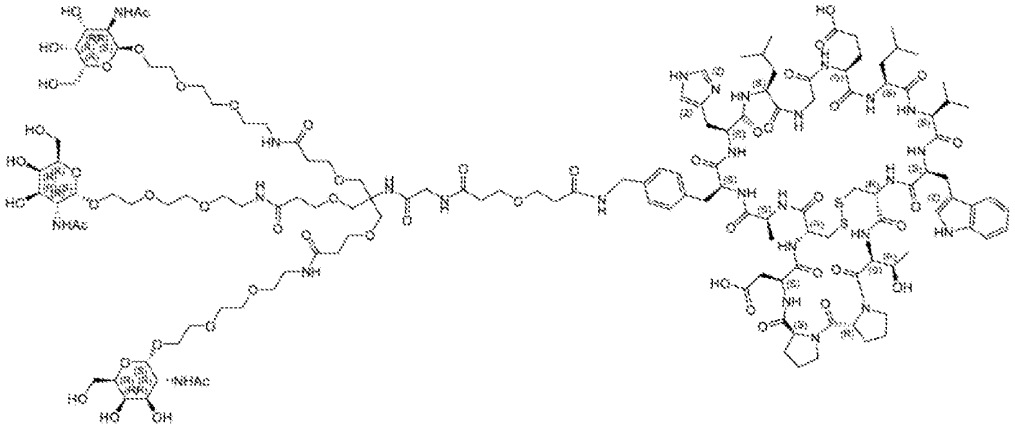
Formula II.

12. The method of any of claims 1 to 9, wherein the immunoglobulin G degrader comprises a compound of Formula III, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof:



Formula III.

13. The method of any of claims 1 to 9, wherein the immunoglobulin G degrader comprises a compound of Formula IV, a pharmaceutically acceptable salt thereof, a polymorph thereof, or a hydrate thereof:



Formula IV.

14. The method of any of claims 1 to 13, wherein the immunoglobulin G degrader is administered to the patient in a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the immunoglobulin G degrader.

15. The method of any of claims 1 to 14, wherein the immunoglobulin G degrader is administered subcutaneously.

16. The method of any of claims 1 to 15, wherein the patient has been exposed to the monoclonal antibody drug prior to the treatment and experienced a reduced efficacy of the monoclonal antibody drug, a side effect, or a combination thereof, due to the formation of the anti-drug antibody.

17. The method of any of claims 1 to 16, further comprising forming a binary complex between the monoclonal antibody drug and tumor necrosis factor alpha, and removing the binary complex from circulation upon the administration of the immunoglobulin G degrader.

18. The method of claim 17, wherein the administration of the immunoglobulin G degrader results in formation of a ternary complex between the monoclonal antibody drug, tumor necrosis factor alpha, and the immunoglobulin G degrader, and wherein the ternary complex is removed from circulation through asialoglycoprotein receptors of hepatocytes.

19. The method of any of claims 1 to 18, further comprising forming a binary complex between the anti-drug antibody and the monoclonal antibody drug, and removing the binary complex from circulation upon the administration of the immunoglobulin G degrader.

20. The method of claim 19, wherein the administration of the immunoglobulin G degrader results in formation of a ternary complex between the anti-drug antibody, the monoclonal antibody drug, and the immunoglobulin G degrader, and wherein the ternary complex is removed from circulation through asialoglycoprotein receptors of hepatocytes.

21. The method of any of claims 1 to 20, wherein the disease or condition is an autoimmune disease, an inflammatory disease, cancer, or a combination thereof.

22. The method of any of the claims 1 to 21, wherein the disease or condition is rheumatoid arthritis, ankylosing spondylitis, psoriasis, juvenile idiopathic arthritis, non-radiographic axial spondyloarthritis, uveitis, psoriatic arthritis, Crohn's disease, systemic lupus erythematosus, Alzheimer's disease, atherosclerosis, heart disease, stroke, or a combination thereof.

23. A method of restoring a therapeutic activity of a monoclonal antibody drug in a patient, the method comprising: administering to the patient a therapeutically effective amount of an immunoglobulin G degrader, wherein the immunoglobulin G degrader is effective to bind to an anti-drug antibody induced by the monoclonal antibody drug.

24. The method of claim 23, further comprising testing the patient to confirm that the anti-drug antibody is present in the patient prior to the administration of the immunoglobulin G degrader.

25. The method of claim 23 or claim 24, wherein the monoclonal antibody drug is a Fc-containing biologic comprising adalimumab, ravulizumab, eculizumab, inebilizumab, ocrelizumab, ofatumumab, rituximab, satralizumab, tocilizumab, or a combination thereof, and the immunoglobulin G degrader is a bifunctional compound having a circulating protein binding moiety (CPBM) linked to a cellular receptor binding moiety (CRBM) via a linker,

wherein the CPBM is an immunoglobulin G binding moiety, and the CRBM is an asialoglycoprotein receptor binding moiety.

26. The method of any of claims 23 to 25, wherein the immunoglobulin G degrader is administered to the patient at a dose of 10 mg/kg to 200 mg/kg.

27. A kit for treating a patient afflicted with a disease or condition in which a monoclonal antibody drug is clinically relevant, the kit including: (a) the monoclonal antibody drug; and (b) instructions for administering the monoclonal antibody with an IgG degrader by one of the methods of claims 1 to 22.

28. A kit for treating a patient afflicted with a disease or condition in which a monoclonal antibody drug is clinically relevant, the kit including: (a) the monoclonal antibody drug; and (b) instructions for restoring a therapeutic activity of a monoclonal antibody drug by one of the methods of claims 23 to 26.