SUMMARY

[0007] A useful tolerogenic drug would consist of an antigen and a tolerance inducing component. The tolerance inducing component can be a chemical conjugated entity, part of a fusion protein, nanoparticles, or cells that are pulsed with the antigen. Ideally, a tolerance-inducing drug is based on the drug it tries to tolerize against, and can easily be modified.

[0008] Disclosed herein are compositions and methods for inducing tolerance towards therapeutic proteins, *e.g.*, protein-based drugs. In some aspects, the present disclosure provides therapeutic, polymer-tethered antigens that include mannose monomers or derivatives thereof. In some embodiments, derivatives of mannose include optionally substituted mannose substituents. In several embodiments, the mannose derivative comprises a mannose with a phosphate at the C1, C2, C3, C4, C5, and/or C6 position. In several embodiments, the targeting moiety comprises mannose-6-phosphate. In some embodiments, compositions including a mannose or mannose-derived moiety induce tolerance to immunogenic protein-based therapeutics, delete antigen-specific CD4 and CD8 T cells, elevate levels of regulatory T cell responses and IL-10 producing Breg cells, and/or reduce antigen-specific plasma cells and memory B cells. The compositions disclosed herein may be targeted for delivery to antigen-presenting cells including, but not limited to, hepatocytes, LSECs, Kupffer cells, and stellate cells. In some aspects, the compositions disclosed herein exhibit affinity for and specifically bind to mannose-binding receptors.

[0008a] In one aspect, provided herein is a compound of Formula 1:

$$X—[Y(Z)_p]_m—R^2$$

Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

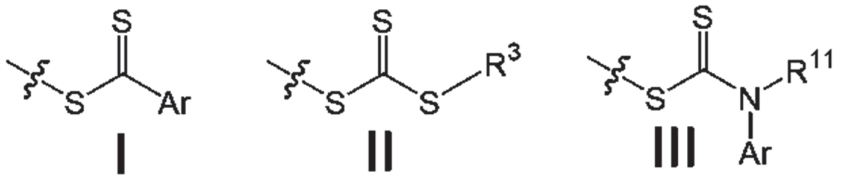
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages;

p is an integer from 2 to 250;

m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



where Ar is a substituted or unsubstituted aromatic group,

R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group.

[0008b] In another aspect, provided herein is a composition comprising the compound as described herein.

[0008c] In another aspect, provided herein is a use of the compound as described herein, in the manufacture of a medicament for inducing tolerance to the antigen, the tolerogenic portion thereof, or the mimetic thereof.

[0008d] In another aspect, provided herein is a use of a composition Formula 1:

$$X—[Y(Z)_p]_m—R^2$$

Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

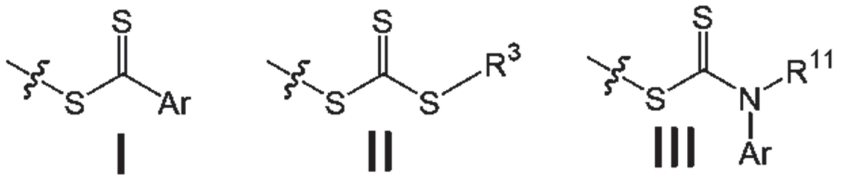
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor;

p is an integer from 2 to 250;

m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



where Ar is a substituted or unsubstituted aromatic group, R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group, in the manufacture of a medicament for inducing immunological tolerance to an antigen target, wherein the medicament is to be administered to a subject.

[0008e] In another aspect, provided herein is a use of a composition comprising a compound of Formula 1:

$$X—[Y(Z)_p]_m—R^2$$

Formula 1

wherein:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

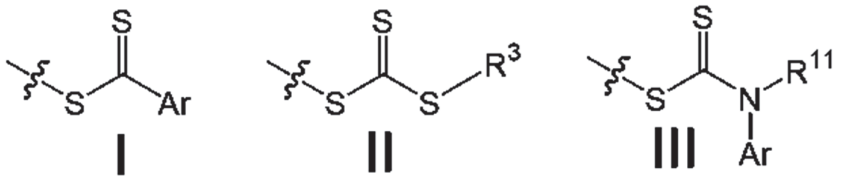
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages;

p is an integer from 2 to 250;

m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



where Ar is a substituted or unsubstituted aromatic group, R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group; in the manufacture of a

medicament for treating or preventing an unwanted immune response against an antigen, wherein the medicament is to be administered to a subject in need of suppression of an immune response to the antigen, wherein the unwanted immune response is transplant rejection, immune response against a therapeutic agent, autoimmune disease, allergy or hypersensitivity, or a combination thereof.

[0008f] In another aspect, provided herein is a use of the as described herein, in the manufacture of a medicament for the treatment of multiple sclerosis.

[0008g] In another aspect, provided herein is a use of a composition comprising the compound as described herein in the manufacture of a medicament for treating or preventing multiple sclerosis, wherein the medicament is to be administered to a subject having, or predicted to have, multiple sclerosis.

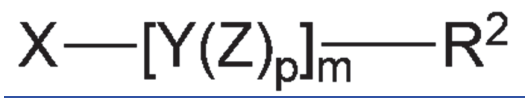
[0008h] In another aspect, provided herein is a use of the compound as described herein, in the manufacture of a medicament for the treatment of Type 1 Diabetes.

[0008i] In another aspect, provided herein is a use of a composition comprising the compound as described herein in the manufacture of a medicament for treating or preventing Type 1 Diabetes, wherein the medicament is to be administered to a subject having, or predicted to have, Type 1 Diabetes.

[0008j] In another aspect, provided herein is a use of the compound as described herein in the manufacture of a medicament for the treatment of Celiac disease.

[0008k] In another aspect, provided herein is a use of a composition comprising the compound as described herein in the manufacture of a medicament for treating or preventing celiac disease, wherein the medicament is to be administered to a subject having, or predicted to have, celiac disease.

[0008l] In another aspect, provided herein is a compound of Formula 1:



Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

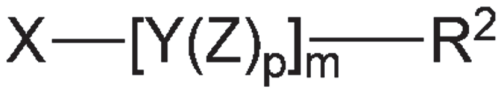
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages; and

R^2 is a reversible addition-fragmentation chain transfer (RAFT) agent.

[0008m] In another aspect provided herein is a compound as described herein, or a composition comprising a compound as described herein for use in therapy.

[0009] In several embodiments, there are provided compounds, as well as compositions comprising such compounds, of Formula 1:

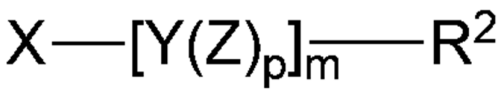


Formula 1

where X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof, Y comprises a linker moiety, Z comprises a moiety that specifically targets a mannose receptor, p is an integer from about 2 to about 250, m is an integer from about 1 to about 100, and R^2 is any of functional groups I-III:

CLAIMS

1. A compound of Formula 1:



Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

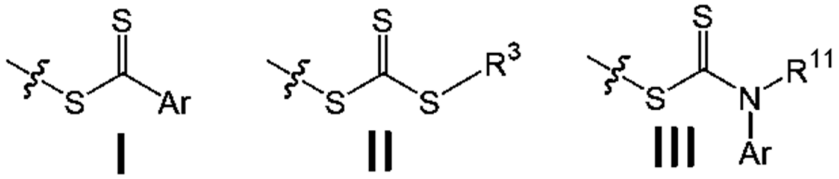
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages;

p is an integer from 2 to 250;

m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



where Ar is a substituted or unsubstituted aromatic group,

R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group.

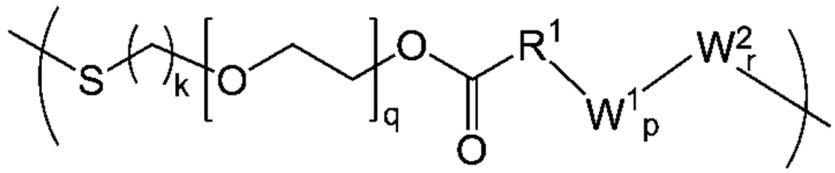
~~2. The compound of claim 1, wherein the moiety that specifically targets a mannose receptor is selected from the group consisting of α linked mannose, β linked mannose, substituted mannose, mannose 6 phosphate, N acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages.~~

~~3.~~2. The compound of claim 1, wherein Y is a linker resulting from reaction of at least one of a N-hydroxysuccinamidyl linker, maleimide linker, PEG linker, vinylsulfone linker, pyridyl

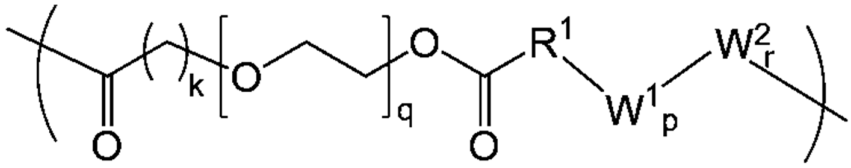
di-thiol-poly(ethylene glycol) linker, pyridyl di-thiol linker, n-nitrophenyl carbonate linker, NHS-ester linker, and nitrophenoxy poly(ethylene glycol)ester linker.

~~4.~~3. The compound of claim ~~3~~2, wherein Y is covalently bound to X.

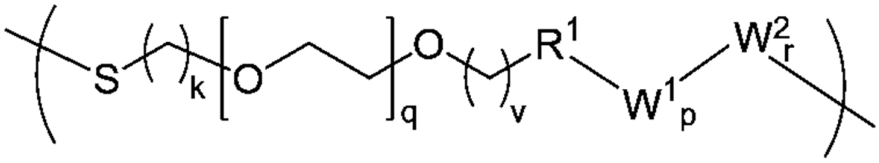
~~5.~~4. The compound of claim 1, wherein -[$Y(Z)_p$]- is represented by one of Formula Ya to Yr:



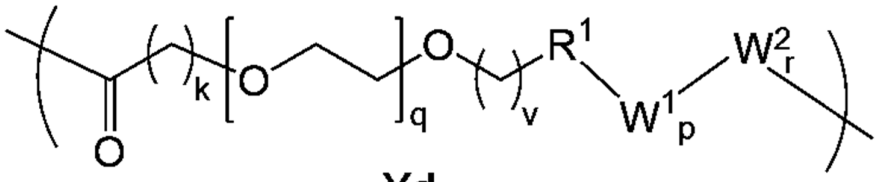
Ya



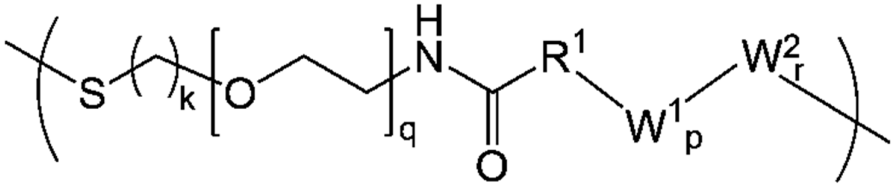
Yb



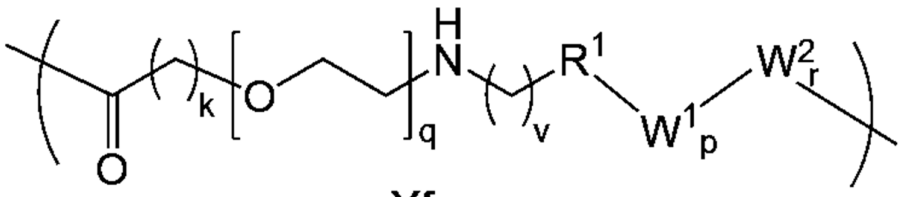
Yc



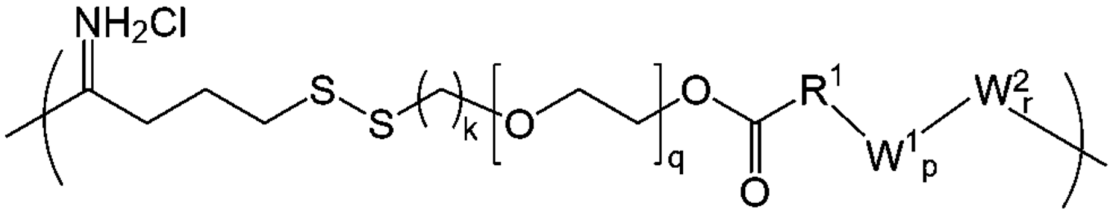
Yd



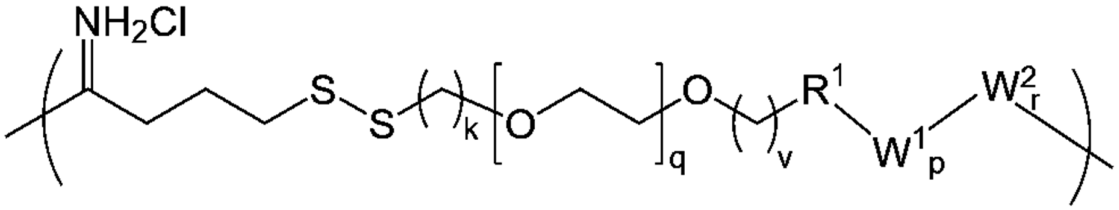
Ye



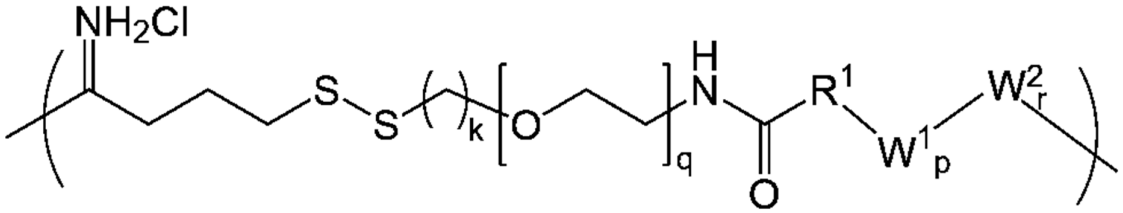
Yf



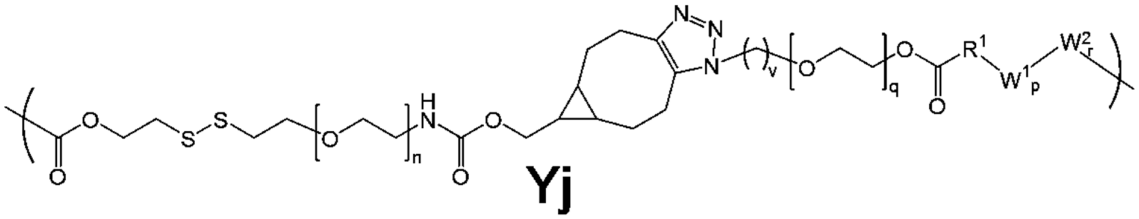
Yg



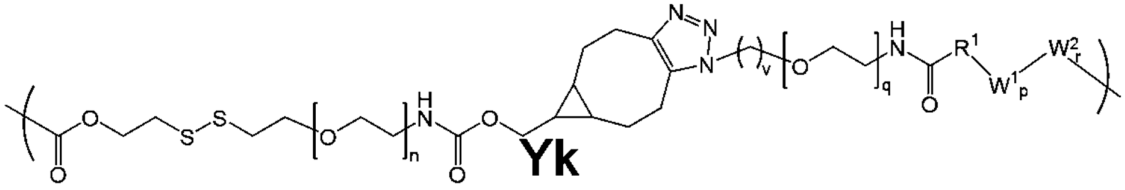
Yh



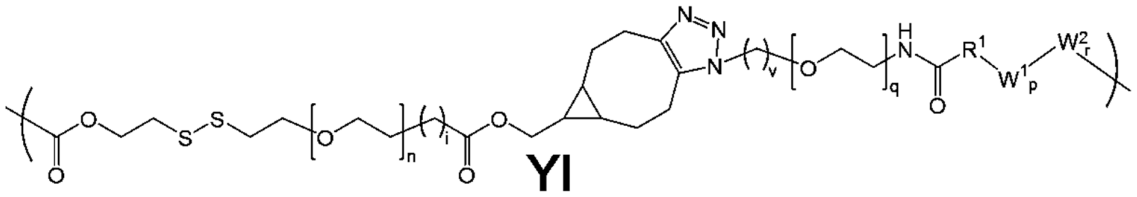
Yi



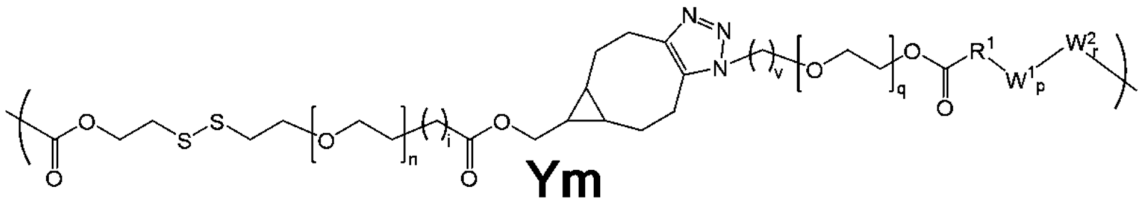
Yj



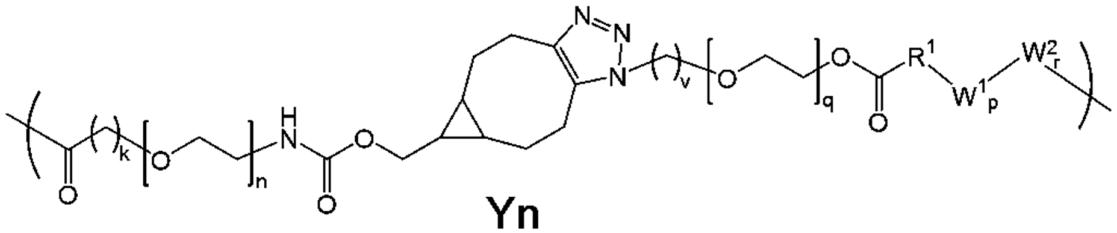
Yk



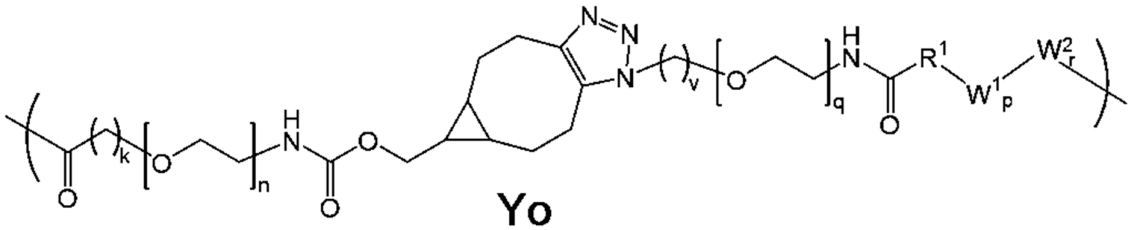
Yl



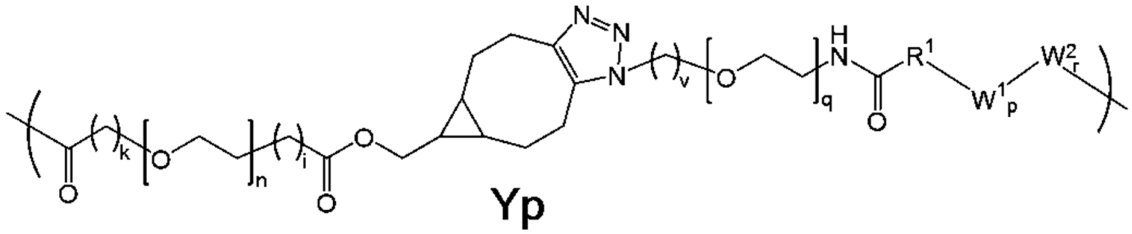
Ym



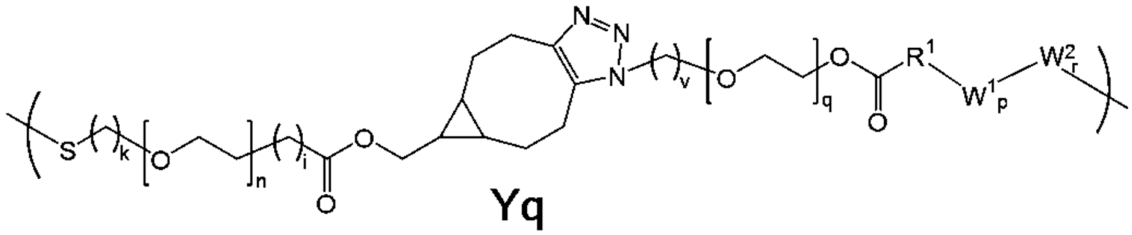
Yn



Yo

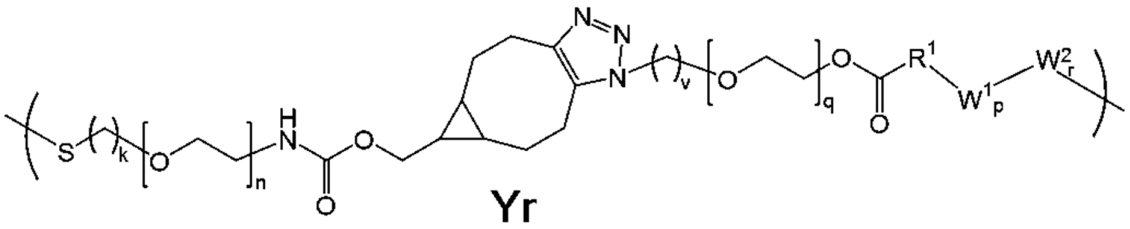


Yp



Yq

and



where

n is an integer from 1 to 100;

q is an integer from 1 to 44;

k is an integer from 1 to 12;

i is an integer from 0 to 20;

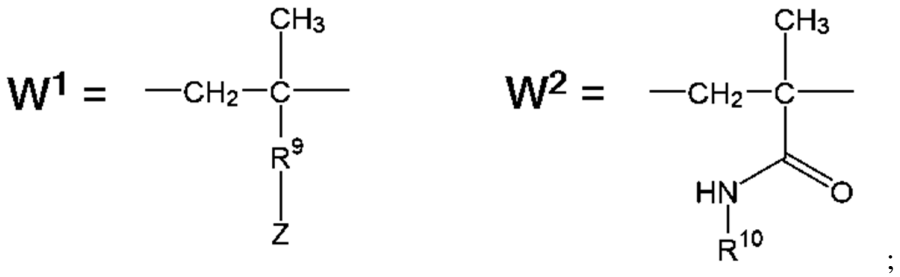
v is an integer from 1 to 4;

p is an integer from 2 to 250;

r is an integer from 0 to 250;

R_1 is $-CH_2-$, $-(CH_2)_2-C(CH_3)(CN)-$, $-(CH_2)_2-C(CH_3)(CH_3)-$, $-(CH_2)_2-CH(CH_3)-$ or $-CH(CH_3)-$;

W^1 and W^2 are as defined below:



;

R^9 is a direct bond, -(CH2)2-NH-C(O)- (an ethylaceetamido group or "EtAcN") or -(CH2)2-(O-CH2-CH2)t-NH-C(O)- (a pegylated ethylacetamido group or "Et-PEGt-AcN")

t is an integer from 1 to 5;

Z is mannose or a mannose receptor-targeting moiety selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages; and

R^{10} is an aliphatic group, an alcohol, an aliphatic amine-containing group, or an aliphatic alcohol.

~~6.~~5. The compound of claim 1, wherein Y is an antibody, antibody fragment, peptide or other ligand that binds to X.

~~7.~~6. The compound of claim 1, wherein X is an antigen against which a patient may develop or has developed an unwanted immune response.

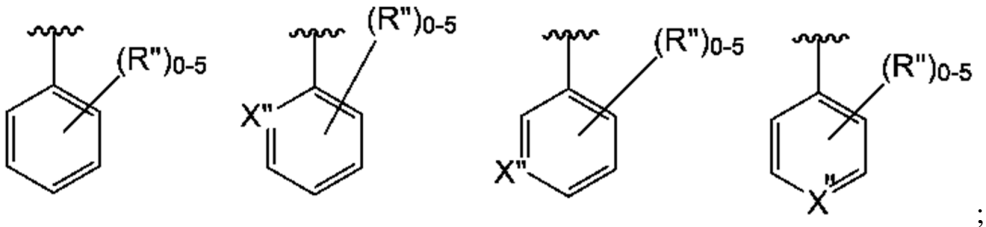
~~8.~~7. The compound of claim ~~7~~6, wherein the antigen is a foreign transplant antigen, an alloantigen, an autoimmune antigen, a food antigen, an animal antigen, a plant antigen, an environmental antigen, a therapeutic antigen, a synthetic self-antigen, or a tolerogenic portion thereof.

~~9.~~8. The compound of claim ~~8~~7, wherein X is an asparaginase antigen or an ovalbumin antigen.

~~10.~~9. The compound of claim 1, wherein the mannose receptor is mannose-6-phosphate receptor.

~~11.~~10. The compound of claim 1, wherein Y and X are connected through a bond configured to cleave when the compound reaches a target area.

~~12.~~11. The compound of claim 1, wherein Ar is selected from:



;

where each instance of R", where present, is independently selected from an optionally substituted $C_{1\text{-}6}$-alkyl, optionally substituted $C_{1\text{-}6}$ alkoxy, optionally substituted amino, OH, or halogen and wherein, X" is a heteroatom.

~~13.~~12. The compound of claim ~~12~~ 11 wherein X" is N.

~~14.~~13. The compound of claim 1, wherein R^{11} is $C_{1\text{-}6}$-alkyl.

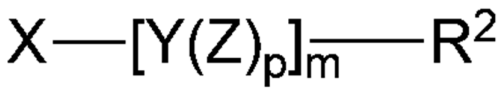
~~15.~~14. The compound of claim 1, wherein R^{11} is $–CH_3$.

~~16.~~15. The compound of claim 1, wherein R^3 is $C_{1\text{-}6}$-alkyl.

~~17.~~16. A composition comprising the compound of any one of claims 1 to 16.

~~18.~~17. Use of the compound of any one of claims 1 to 16, in the manufacture of a medicament for inducing tolerance to the antigen, the tolerogenic portion thereof, or the mimetic thereof.

~~19.~~18. Use of a composition Formula 1:



Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

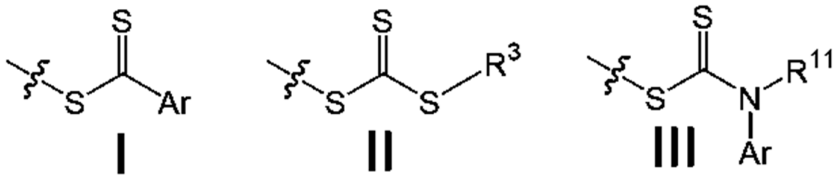
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor;

p is an integer from 2 to 250;

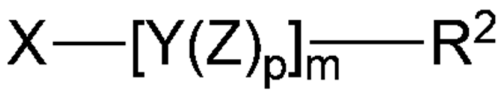
m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



where Ar is a substituted or unsubstituted aromatic group, R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group, in the manufacture of a medicament for inducing immunological tolerance to an antigen target, wherein the medicament is to be administered to a subject.

~~20~~19. Use of a composition comprising a compound of Formula 1:



Formula 1

wherein:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

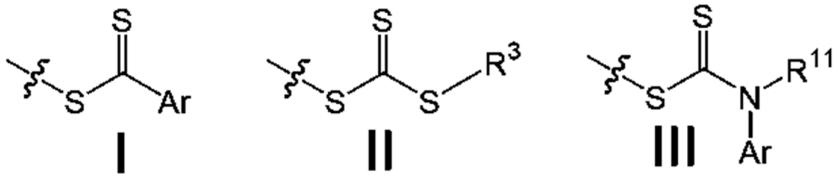
Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages;

p is an integer from 2 to 250;

m is an integer from 1 to 100;

R^2 is any of functional groups I-III:



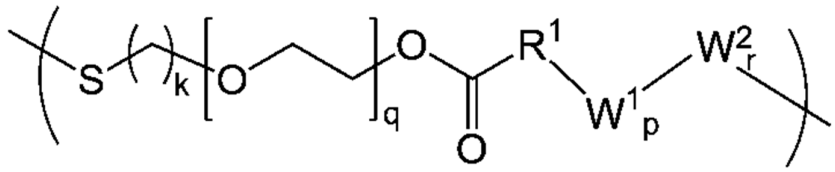
where Ar is a substituted or unsubstituted aromatic group, R^3 is any carbon-containing linear or heterocyclic moiety, and R^{11} is hydrogen or an alkyl group; in the manufacture of a medicament for treating or preventing an unwanted immune response against an antigen, wherein the medicament is to be administered to a subject in need of suppression of an immune response to the antigen, wherein the unwanted immune response is transplant rejection, immune response against a therapeutic agent, autoimmune disease, allergy or hypersensitivity, or a combination thereof.

~~21. The use of claim 19 or 20, wherein the moiety that specifically targets a mannose receptor is selected from the group consisting of α linked mannose, β linked mannose, substituted mannose, mannose 6 phosphate, N acetyl mannosamine, and mannan having β(1 4), α(1 6), α(1 2), and/or α(1 3) linkages.~~

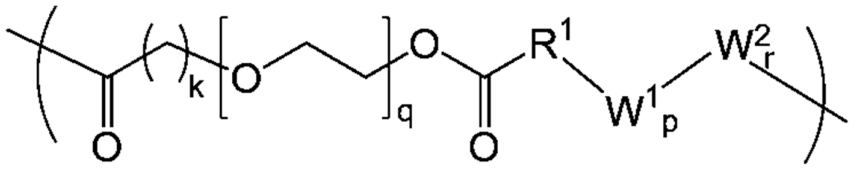
~~22~~20. The use of any one of claims ~~19~~ 18 to ~~21~~19, wherein Y is a linker resulting from reaction of at least one of a N-hydroxysuccinamidyl linker, PEG linker, maleimide linker, vinylsulfone linker, pyridyl di-thiol-poly(ethylene glycol) linker, pyridyl di-thiol linker, n-nitrophenyl carbonate linker, NHS-ester linker, and nitrophenoxy poly(ethylene glycol)ester linker.

~~23~~21. The use of any of claims ~~19~~ 18 to ~~22~~20, wherein Y is covalently bound to X.

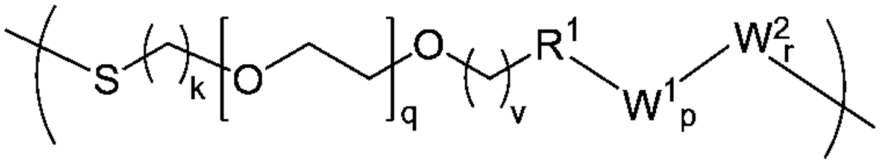
~~24~~22. The use of any of claims ~~19~~ 18 to ~~23~~21, wherein -[$Y(Z)_p$]- is represented by one of Formula Ya to Yr:



Ya



Yb



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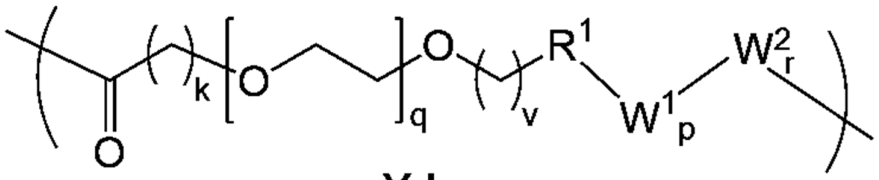

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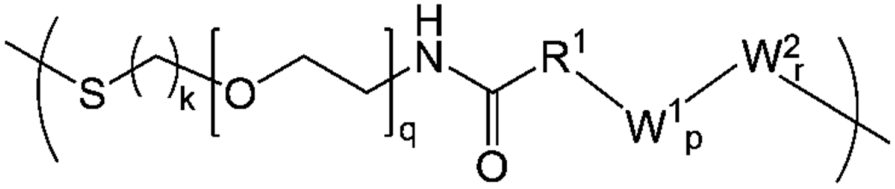

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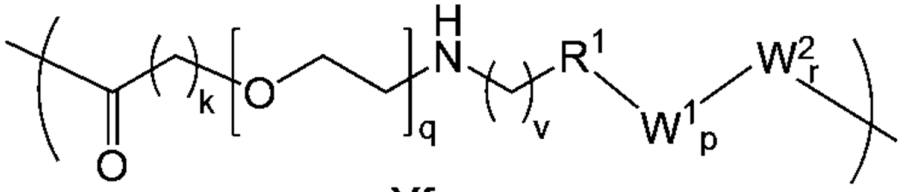
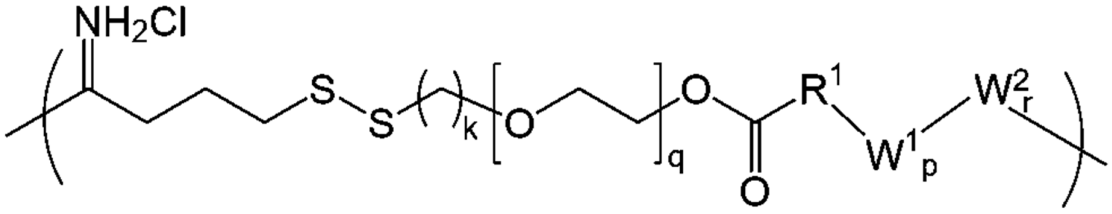
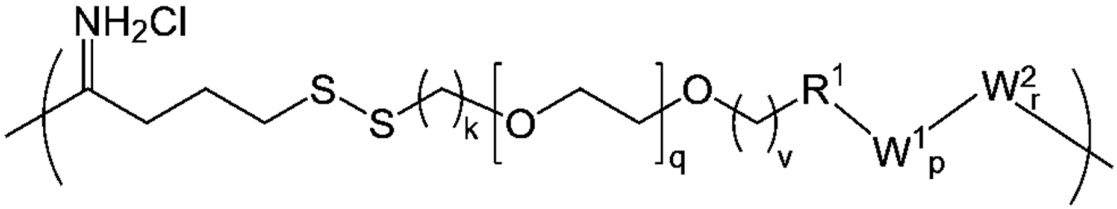


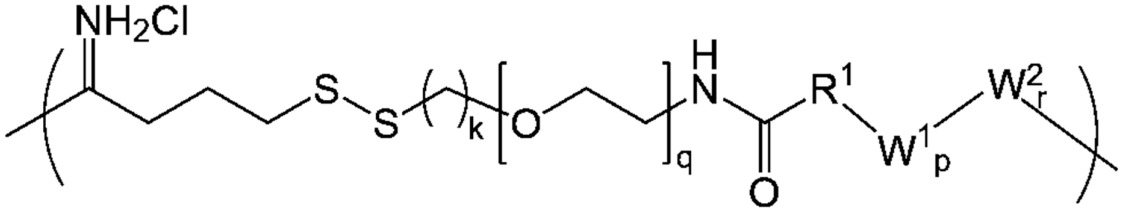
Yf



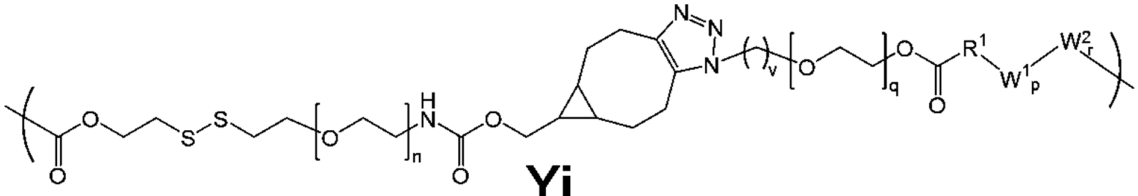
Yg



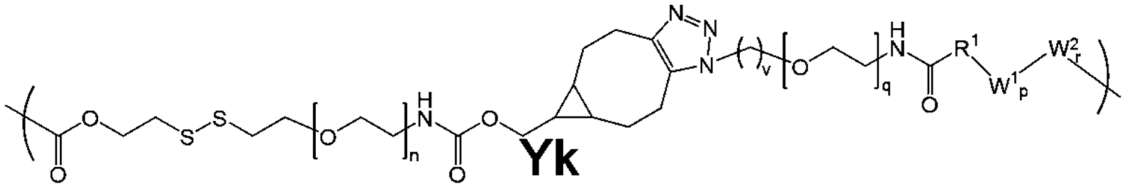
Yh



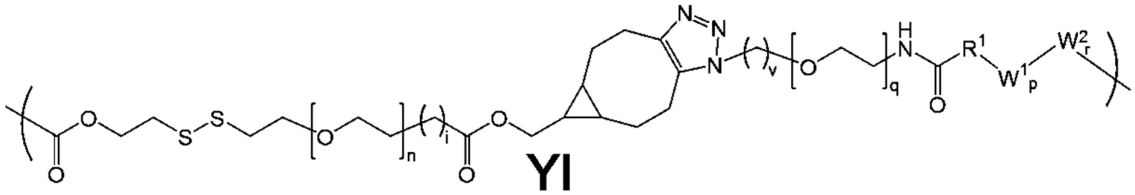
Yi



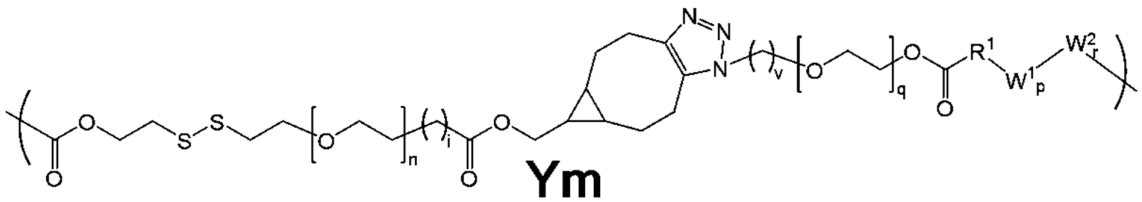
Yj



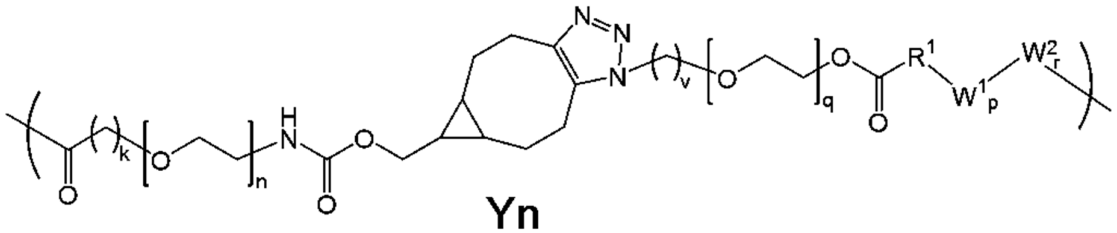
Yk



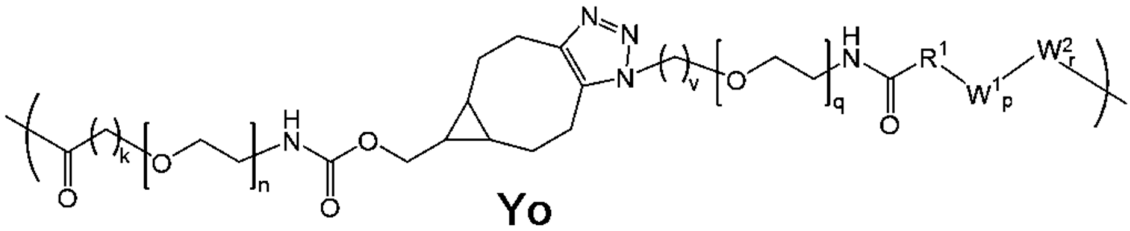
Yl



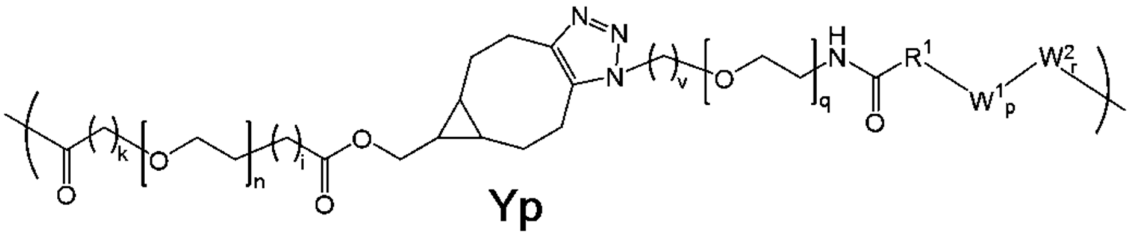
Ym



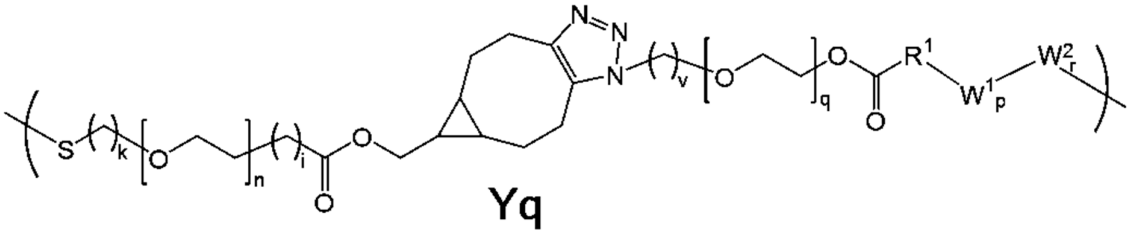
Yn



Yo

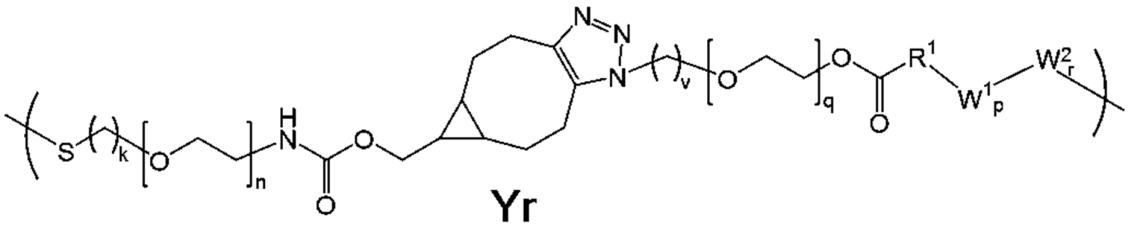


Yp



Yq

and



Yr

wherein

n is an integer from 1 to 100;

q is an integer from 1 to 44;

k is an integer from 1 to 12;

i is an integer from 0 to 20;

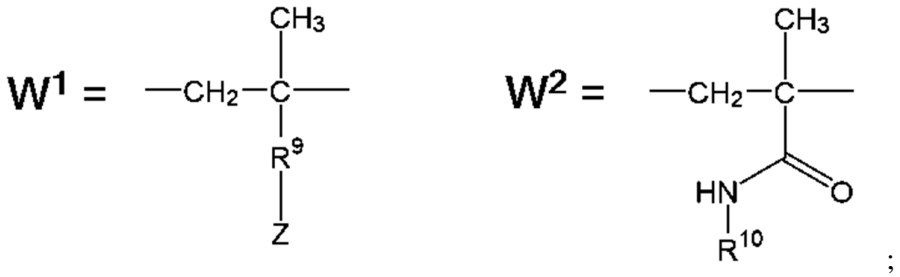
v is an integer from 1 to 4;

p is an integer from 2 to 250;

r is an integer from 0 to 250;

R_1 is $-CH_2-$, $-(CH_2)_2-C(CH_3)(CN)-$, $-(CH_2)_2-C(CH_3)(CH_3)-$, $-(CH_2)_2-CH(CH_3)-$ or $-CH(CH_3)-$;

W^1 and W^2 are as defined below:



;

R^9 is a direct bond, -(CH2)2-NH-C(O)- (an ethylaceetamido group or "EtAcN") or -(CH2)2-(O-CH2-CH2)t-NH-C(O)- (a pegylated ethylacetamido group or "Et-PEGt-AcN")

t is an integer from 1 to 5;

Z is mannose or a mannose receptor-targeting moiety selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages; and

R10 is an aliphatic group, an alcohol, an aliphatic amine-containing group, or an aliphatic alcohol.

~~25~~23. The use of any one of claims ~~19~~ 18 to ~~24~~22, wherein Y is an antibody, antibody fragment, peptide or other ligand that binds to X.

~~26~~24. The use of any of claims ~~19~~ 18 to ~~25~~23, wherein X is an antigen against which a patient may develop or has developed an unwanted immune response.

~~27~~25. The use of any one of claims ~~19~~ 18 to ~~26~~24, wherein the antigen is a foreign transplant antigen, an alloantigen, an autoimmune antigen, a food antigen, an animal antigen, a plant antigen, an environmental antigen, a therapeutic agent, a synthetic self-antigen, or a tolerogenic portion thereof.

~~28~~26. The use of any one of claims ~~19~~ 18 to ~~27~~25, wherein the antigen is comprised in a vesicle, cell fragment, or cell.

~~29~~27. The use of any one of claims ~~19~~ 18 to ~~28~~26, wherein X is an asparaginase antigen or an ovalbumin antigen.

~~30~~28. The use of any one of claims ~~19~~ 18 to ~~29~~27, wherein the mannose receptor is mannose-6-phosphate receptor.

~~31~~29. The use of any one of claims ~~19~~ 18 to ~~30~~28, wherein Y and X are connected through a bond configured to cleave when the compound reaches a target area.

~~32~~30. The compound according to any one of claims 1 to ~~8~~ 7 and ~~10~~ 9 to 165, wherein the antigen comprises at least one autoimmune antigen or tolerogenic portion thereof.

~~33~~31. The compound of claim ~~32~~30, wherein the at least one autoimmune antigen comprises at least one of an immunogenic fragment or fragments of myelin basic protein (MPB), an immunogenic fragment or fragments of myelin oligodendrocyte glycoprotein (MOG), an immunogenic fragment or fragments of myelin proteolipid protein (PLP), MBP, MOG, or PLP.

~~34~~32. The compound of claim ~~33~~31, wherein the at least one autoimmune antigen comprises at least one of SEQ ID Nos. 23-47.

~~35~~33. The compound of claim ~~33~~31, wherein the at least one autoimmune antigen comprises at least one of SEQ ID Nos. 24, 25, 27, 28, 31, 32, 33, 34, 35, 36, 43, 44, 45, 46, and 47.

~~36~~34. The compound of claim ~~35~~33, further comprising at least one of SEQ ID NOs: 29, 38, 39, 40, 41, and 42.

~~37~~35. Use of the compound of any one of claims ~~32~~30 to ~~36~~33, in the manufacture of a medicament for the treatment of multiple sclerosis.

~~38~~36. Use of a composition comprising the compound according to any one of claims ~~32~~30-~~36~~ 34 in the manufacture of a medicament for treating or preventing multiple sclerosis, wherein the medicament is to be administered to a subject having, or predicted to have, multiple sclerosis.

~~39~~37. The compound of claim ~~32~~30, wherein the at least one autoimmune antigen comprises at least one of insulin, proinsulin, preproinsulin, glutamic acid decarboxylase-65 (GAD-65 or glutamate decarboxylase 2), GAD-67, glucose-6 phosphatase 2, islet-specific glucose 6 phosphatase catalytic subunit related protein (IGRP), insulinoma-associated protein 2 (IA-2), insulinoma-associated protein 2β (IA-2β), ICA69, ICA12 (SOX-13), carboxypeptidase H, Imogen 38, GLIMA 38, chromogranin-A, HSP-60, carboxypeptidase E, peripherin, glucose transporter 2, hepatocarcinoma-intestine-pancreas/pancreatic associated protein, S100β, glial fibrillary acidic protein, regenerating gene II, pancreatic duodenal homeobox 1, dystrophia myotonica kinase, and SST G-protein coupled receptors 1-5, or an immunogenic fragment of any of these antigens.

~~40~~38. The compound of claim ~~39~~37, wherein the at least one autoimmune antigen comprises at least one of SEQ ID NOs: 1-19, or an immunogenic fragment of any of SEQ ID NOs: 1-19.

~~41~~39. The compound of claim ~~39~~37, wherein the at least one autoimmune antigen comprises at least one of SEQ ID NOs: 4-19.

~~42~~40. Use of the compound of any one of claims ~~39~~37 to ~~41~~39, in the manufacture of a medicament for the treatment of Type 1 Diabetes.

~~43~~41. Use of a composition comprising the compound according to any one of claims ~~39~~37 to ~~41~~ 39 in the manufacture of a medicament for treating or preventing Type 1 Diabetes, wherein the medicament is to be administered to a subject having, or predicted to have, Type 1 Diabetes.

~~44~~42. The compound according to any one of claims 1 to ~~8~~ 7 and ~~10~~ 9 to ~~16~~15, wherein the antigen comprises a food antigen, or a tolerogenic portion thereof.

~~45~~43. The compound of claim ~~44~~42, wherein the antigen comprises at least one of tissue transglutaminase, high molecular weight glutenin, low molecular weight glutenin, gluten, alpha-gliadin, gamma-gliadin, omega-gliadin, hordein, secalin, avenin, and deamidated forms thereof.

~~46~~44. The compound of claim ~~44~~42, wherein the antigen comprises a tolerogenic portion of at least one of tissue transglutaminase, high molecular weight glutenin, low molecular weight glutenin, gluten, alpha-gliadin, gamma-gliadin, omega-gliadin, hordein, secalin, avenin, and deamidated forms thereof.

~~47~~45. The compound of claim ~~46~~44, wherein the antigen comprises at least one of SEQ ID NOs. 54-61.

~~48~~46. Use of the compound of any one of claims ~~44~~42 to ~~47~~ 45 in the manufacture of a medicament for the treatment of Celiac disease.

~~49~~47. Use of a composition comprising the compound according to any one of claims ~~44~~42 to ~~47~~ 45 in the manufacture of a medicament for treating or preventing celiac disease, wherein the medicament is to be administered to a subject having, or predicted to have, celiac disease.

~~50~~48. The compound according to any one of claims 1 to ~~8~~ 7 and ~~10~~ 9 to ~~16~~15, wherein the antigen comprises a protein therapeutic or a tolerogenic portion thereof.

~~51~~49. The compound according to claim ~~50~~48, wherein the antigen is selected from the group consisting of Adalimumab, Adenosine deaminase, Ado-trastuzumab emtansine, Agalsidase alfa, Agalsidase beta, Aldeslukin, Alglucerase, Alglucosidase alfa, a-1-proteinase inhibitor, Anakinra, Anistreplase, Antithrombin III, Antithymocyte globulin, Ateplase, Bevacizumab, Bivalirudin, Botulinum toxin type A, Botulinum toxin type B, Cl-esterase inhibitor, Canakinumab, Carboxypeptidase G2, Certolizumab pegol, Cetuximab, Collagenase, Crotalidae immune Fab, Darbepoetin-a, Denosumab, Digoxin immune Fab, Domase alfa, Eculizumab, Etanercept, Factor VIia, Factor VIII, Factor IX, Factor XI, Factor **XIII,**

Fibrinogen, Filgrastim, Galsulfase, Golimumab, Histrelin acetate, Hyaluronidase, Idursulphase, Imiglucerase, Infliximab, Interferon-α2a, Interferon-α2b, Interferon-β1a, Interferon-β1b, Interferon-γ1b, Ipilimumab, Larginase, L-asparaginase, L-methionase, Lactase, Laronidase, Lepirudin, Mecasermin, Mecasermin rinfabate, Methoxy Natalizumab, Octreotide, Ofatumumab, Oprelvekin, Pancreatic amylase, Pancreatic lipase, Papain, Peg-asparaginase, Peg-doxorubicin HCl, PEG-epoetin-β, Pegfilgrastim, Peg-Interferon-α2a, Peg-Interferon-α2b, Pegloticase, Pegvisomant, Phenylalanine ammonia-lyase (PAL), Protein C, Rasburicase (uricase), Sacrosidase, Salmon calcitonin, Sargramostim, Streptokinase, Tenecteplase, Teriparatide, Tocilizumab (atlizumab), Trastuzumab, Type 1 alpha-interferon, Ustekinumab, vW factor..

~~52~~50. A compound of Formula 1:

$$X—[Y(Z)_p]_m——R^2$$

Formula 1

where:

X comprises an antigen, a tolerogenic portion thereof, or a mimetic thereof;

Y comprises a linker moiety;

Z comprises a moiety that specifically targets a mannose receptor selected from the group consisting of α-linked mannose, β-linked mannose, substituted mannose, mannose-6-phosphate, N-acetyl mannosamine, and mannan having β(1-4), α(1-6), α(1-2), and/or α(1-3) linkages; and

R^2 is a reversible addition-fragmentation chain transfer (RAFT) agent.

~~53~~51. A compound of any one of claims 1 to ~~16~~15, ~~32~~30 to ~~36~~34, ~~39~~37 to ~~41~~ 39 or ~~44~~42 to ~~47~~45, or a composition comprising a compound of any one of claims 1 to 15, 30 to 34, 37 to 39 or 42 to 45 ~~1-16, 32-36, 39-41 or 44-47~~ for use in therapy.