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AVISO DE NOTIFICACION
CORREO CERTIFICADO



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Trámite : 11 PATENTEIYII
Evento : 378 FASENACIONALI
Actuación : 432 COMUNICACTOADM
Destinatario : CARLOS REYNALDO OLARTE GARCIA Folios 1

Señor (a) (es)
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DIAGONAL 34 No. 5-28
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Referencia RESOLUCION : 5007
Fecha : 29/01/2010
Expediente : 7-21337
Trámite : 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II
Evento : 378 FASE NACIONAL INCLUIDO CAPITULO I
Actuación : 432 COMUNICACION ACTO ADMINISTRATIVO

Comendidamente le solicito presentarse a este Despacho ubicado en la Carrera 13 No. 27 - 00 Piso Quinto (5), de la ciudad de Bogotá D.C., dentro del término de cinco (5) días hábiles contados a partir del envío de la presente citación, en horario de 8:00 a.m. a 4:30 p.m. jornada continua, con el fin de notificarle personalmente el contenido de la resolución de la referencia proferida dentro del expediente tramitado con el número de radicación citado en el asunto.

De no hacerse presente en el término indicado anteriormente, la providencia en mención se notificará por edicto, el cual se fijará por el término de diez (10) días en el Centro de Documentación e Información.

Para su comodidad el texto completo de la resolución se encontrará disponible en la página web de la Entidad desde el día hábil siguiente al de su notificación, la cual podrá ser consultada desde un computador con acceso a Internet, en la página www.sic.gov.co, con el número de resolución a través de la opción servicios en línea bases de datos - otros servicios - consulta actos administrativos.

En caso de que se haya notificado, haga caso omiso de este aviso.

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 000007

Por la cual se niega una patente de invención

Rad. PCT/07-21337

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

En ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "TERAPIA DE COMBINACION UTILIZANDO PROTEINAS DE FUSION DE TRANSFERRINA QUE COMPRENDEN GLP-1", que corresponde a la solicitud internacional PCT/US2005/027800 de fecha 03 de agosto del 2005, fue radicada en esta Superintendencia el 02 de marzo del 2007 bajo el número 07-021337 -00000-0000, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales. (...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente"*.

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 338 a 347 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del solicitante, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION de 19007

Por la cual se niega una patente de invención

Rad. PCT/07-21337

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "TERAPIA DE COMBINACION UTILIZANDO PROTEINAS DE FUSION DE TRANSFERRINA QUE COMPRENDEN GLP-1", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente al doctor Carlos Reinaldo Olarte García, en su calidad de apoderado de BIOREXIS PHARMACEUTICAL CORPORATION., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 29 ENE. 2010

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


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US 20030221201A1

(19) **United States**(12) **Patent Application Publication**
Prior et al.(10) **Pub. No.: US 2003/0221201 A1**(43) **Pub. Date: Nov. 27, 2003**(54) **MODIFIED TRANSFERRIN FUSION
PROTEINS**(75) **Inventors: Christopher P. Prior, King of Prussia,
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CORPORATION**(21) **Appl. No.: 10/378,094**(22) **Filed: Mar. 4, 2003****Related U.S. Application Data**(63) **Continuation-in-part of application No. 10/231,494,
filed on Aug. 30, 2002.**(60) **Provisional application No. 60/315,745, filed on Aug.
30, 2001. Provisional application No. 60/334,059,
filed on Nov. 30, 2001. Provisional application No.
60/406,977, filed on Aug. 30, 2002.****Publication Classification**(51) **Int. Cl.⁷ A61K 38/21; A61K 38/40;
A01K 67/027; C07K 14/79**(52) **U.S. Cl. 800/7; 530/351; 530/350;
530/400; 424/85.5; 514/6**(57) **ABSTRACT**

Modified fusion proteins of transferrin and therapeutic proteins or peptides including soluble toxin receptors, with increased serum half-life or serum stability are disclosed. Preferred fusion proteins include those modified so that the transferrin moiety exhibits no or reduced glycosylation, binding to iron and/or binding to the transferrin receptor.

MODIFIED TRANSFERRIN FUSION PROTEINS

RELATED APPLICATIONS

[0001] This application is a Continuation-In-Part Application of 10,231,494, filed Aug. 30, 2002, which claims the benefit of U.S. Provisional Application 60/315,745, filed Aug. 30, 2001 and U.S. Provisional Application 60/334,059, filed Nov. 30, 2001, all of which are herein incorporated by reference in their entirety. This application also claims the benefit of U.S. Provisional Application 60/406,977, filed Aug. 30, 2002, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to therapeutic proteins or peptides and soluble toxin receptor fragments with extended serum stability or serum half-life fused to or inserted in a transferrin molecule modified to reduce or inhibit glycosylation, iron binding and/or transferrin receptor binding. Specifically, the present invention includes IFN- β , GLP-1, EMP1, and T-20 fused to or inserted in a transferrin molecule or a modified transferrin molecule. The present invention also includes an anti-toxin fusion protein comprising a fragment of synaptotagmin I fused to or inserted in a transferrin molecule or a modified transferrin molecule.

BACKGROUND OF THE INVENTION

[0003] Therapeutic proteins or peptides in their native state or when recombinantly produced are typically labile molecules exhibiting short periods of serum stability or short serum half-lives. In addition, these molecules are often extremely labile when formulated, particularly when formulated in aqueous solutions for diagnostic and therapeutic purposes.

[0004] Few practical solutions exist to extend or promote the stability in vivo or in vitro of proteinaceous therapeutic molecules. Polyethylene glycol (PEG) is a substance that can attach to a protein, resulting in longer-acting, sustained activity of the protein. If the activity of a protein is prolonged by the attachment to PEG, the frequency that the protein needs to be administered is decreased. PEG attachment, however, often decreases or destroys the protein's therapeutic activity.

[0005] Therapeutic proteins or peptides have also been stabilized by fusion to a heterologous protein capable of extending the serum half-life of the therapeutic protein. For instance, therapeutic proteins fused to albumin and antibody fragments may exhibit extended serum half-life when compared to the therapeutic protein in the unfused state. See U.S. Pat. Nos. 5,876,969 and 5,766,88.

[0006] Another serum protein, glycosylated human transferrin (Tf) has also been used to make fusions with therapeutic proteins to target delivery intracellularly or to carry heterologous agents across the blood-brain barrier. These fusion proteins comprising glycosylated human Tf have been used to target nerve growth factor (NGF) or ciliary neurotrophic factor (CNTF) across the blood-brain barrier by fusing full-length Tf to the either agent. See U.S. Pat. Nos. 5,672,683 and 5,977,307. In these fusion proteins, the Tf portion of the molecule is glycosylated and binds to two

atoms of iron, which is required for Tf binding to its receptor on a cell and, according to the inventors of these patents, to target delivery of the NGF or CNTF moiety across the blood-brain barrier. Transferrin fusion proteins have also been produced by inserting an HIV-1 protease sequence into surface exposed loops of glycosylated transferrin to investigate the ability to produce another form of Tf fusion for targeted delivery to the inside of a cell via the Tf receptor (Ali et al. (1999) *J. Biol. Chem.* 274(34):24066-24073).

[0007] Serum transferrin (Tf) is a monomeric glycoprotein with a molecular weight of 80,000 daltons that binds iron in the circulation and transports it to various tissues via the transferrin receptor (TfR) (Aisen et al. (1980) *Ann. Rev. Biochem.* 49: 357-393; MacGillivray et al. (1981) *J. Biol. Chem.* 258: 3543-3553, U.S. Pat. No. 5,026,651). Tf is one of the most common serum molecules, comprising up to about 5-10% of total serum proteins. Carbohydrate deficient transferrin occurs in elevated levels in the blood of alcoholics and exhibits a longer half life (approximately 14-17 days) than that of glycosylated transferrin (approximately 7-10 days). See van Eijk et al. (1983) *Clin. Chim. Acta* 132:167-171, Stibler (1991) *Clin. Chem.* 37:2029-2037 (1991), Arndt (2001) *Clin. Chem.* 47(1):13-27 and Stibler et al. in "Carbohydrate-deficient consumption", *Advances in the Biosciences*, (Ed Nordmann et al.), Pergamon, 1988, Vol. 71, pages 353-357).

[0008] The structure of Tf has been well characterized and the mechanism of receptor binding, iron binding and release and carbonate ion binding have been elucidated (U.S. Pat. Nos. 5,026,651, 5,986,067 and MacGillivray et al. (1983) *J. Biol. Chem.* 258(6):3543-3546).

[0009] Transferrin and antibodies that bind the transferrin receptor have also been used to deliver or carry toxic agents to tumor cells as cancer therapy (Baselga and Mendelsohn, 1994), and transferrin has been used as a non-viral gene therapy vector to vehicle to deliver DNA to cells (Frank et al., 1994; Wagner et al., 1992). The ability to deliver proteins to the central nervous system (CNS) using the transferrin receptor as the entry point has been demonstrated with several proteins and peptides including CD4 (Walus et al., 1996), brain derived neurotrophic factor (Pardridge et al., 1994), glial derived neurotrophic factor (Albeck et al.), a vasointestinal peptide analogue (Bickel et al., 1993), a betaamyloid peptide (Saito et al., 1995), and an antisense oligonucleotide (Pardridge et al., 1995).

[0010] Transferrin fusion proteins have not, however, been modified or engineered to extend the serum half-life of a therapeutic protein or peptide or to increase bioavailability by reducing or inhibiting glycosylation of the Tf moiety or to reduce or prevent iron and/or Tf receptor binding.

SUMMARY OF THE INVENTION

[0011] As described in more detail below, the present invention includes modified Tf fusion proteins comprising at least one therapeutic protein, polypeptide or peptide entity, wherein the Tf portion is engineered to extend the serum half-life or bioavailability of the molecule. The invention also includes pharmaceutical formulations and compositions comprising the fusion proteins, methods of extending the serum stability, serum half-life and bioavailability of a therapeutic protein by fusion to modified transferrin, nucleic acid molecules encoding the modified Tf fusion proteins,

and the like. Another aspect of the present invention relates to methods of treating a patient with a modified Tf fusion protein.

[0012] Preferably, the modified Tf fusion proteins comprise a human transferrin Tf moiety that has been modified to reduce or prevent glycosylation and/or iron and receptor binding.

[0013] The present invention provides fusion proteins comprising therapeutic proteins fused to or inserted into the transferrin or modified transferrin molecules. Preferably, the therapeutic proteins of the present invention include β -interferon (β -IFN), glucagon-like peptide (GLP-1), EPO (erythropoietin) mimetic peptide (EMP1), and T-20.

[0014] The present invention also provides fusion proteins comprising a soluble toxin receptor fragment that binds a toxin fused to or inserted into the transferrin or modified transferrin molecules. The soluble toxin receptor may be synaptotagmin 1 and the soluble fragment is amino acids 1-53.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 shows an alignment of the N and C Domains of Human (Hu) transferrin (Tf) with similarities and identities highlighted.

[0016] FIGS. 2A-2B show an alignment of transferrin sequences from different species. Light shading: Similarity; Dark shading: Identity

[0017] FIG. 3 shows the location of a number of Tf surface exposed insertion sites for therapeutic proteins, polypeptides or peptides.

DETAILED DESCRIPTION

[0018] General Description

[0019] The present invention is based in part on the finding by the inventors that therapeutic proteins can be stabilized to extend their serum half-life and/or activity in vivo by genetically fusing the therapeutic proteins to transferrin, modified transferrin, or a portion of transferrin or modified transferrin sufficient to extend the half-life of the therapeutic protein in serum. The modified transferrin fusion proteins include a transferrin protein or domain covalently linked to a therapeutic protein or peptide, wherein the transferrin portion is modified to contain one or more amino acid substitutions, insertions or deletions compared to a wild-type transferrin sequence. In one embodiment, Tf fusion proteins are engineered to reduce or prevent glycosylation within the Tf or a Tf domain. In other embodiments, the Tf protein or Tf domain(s) is modified to exhibit reduced or no binding to iron or carbonate ion, or to have a reduced affinity or not bind to a Tf receptor (TfR).

[0020] The therapeutic proteins contemplated by the present invention include, but are not limited to polypeptides, antibodies, peptides, or fragments or variants thereof. Preferably, the therapeutic proteins of the present invention include β -interferon, glucagon-like peptide-1 (GLP-1), EPO mimetic peptide (EMP1), and T-20.

[0021] The present invention also contemplates anti-toxin fusion proteins comprising a soluble toxin receptor fragment fused or inserted into transferrin or modified transferrin.

Preferably, the soluble toxin receptor fragment binds a specific toxin. In one embodiment, the soluble toxin receptor fragment is amino acids 1-53 (SEQ ID NO: 4) of synaptotagmin 1.

[0022] The present invention therefore includes transferrin fusion proteins, therapeutic compositions comprising the fusion proteins, and methods of treating, preventing, or ameliorating diseases or disorders by administering the fusion proteins. A transferrin fusion protein of the invention includes at least a fragment or variant of a therapeutic protein and at least a fragment or variant of modified transferrin, which are associated with one another, preferably by genetic fusion (i.e., the transferrin fusion protein is generated by translation of a nucleic acid in which a polynucleotide encoding all or a portion of a therapeutic protein is joined in-frame with a polynucleotide encoding all or a portion of modified transferrin) or chemical conjugation to one another. The therapeutic protein and transferrin protein, once part of the transferrin fusion protein, may be referred to as a "portion", "region" or "moiety" of the transferrin fusion protein (e.g., a "therapeutic protein portion" or a "transferrin protein portion").

[0023] In one embodiment, the invention provides a transferrin fusion protein comprising, or alternatively consisting of, a therapeutic protein and a modified serum transferrin protein. In other embodiments, the invention provides a transferrin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment of a therapeutic protein and a modified transferrin protein. In other embodiments, the invention provides a transferrin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active variant of a therapeutic protein and modified transferrin protein. In further embodiments, the invention provides a transferrin fusion protein comprising a therapeutic protein, and a biologically active and/or therapeutically active fragment of modified transferrin. In another embodiment, the therapeutic protein portion of the transferrin fusion protein is the active form of the therapeutic protein.

[0024] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

[0025] Definitions

[0026] As used herein, the term "biological activity" refers to a function or set of activities performed by a therapeutic molecule, protein or peptide in a biological context (i.e., in an organism or an in vitro facsimile thereof). Biological activities may include but are not limited to the functions of the therapeutic molecule portion of the claimed fusion proteins, such as, but not limited to, the induction of extracellular matrix secretion from responsive cell lines, the induction of hormone secretion, the induction of chemotaxis, the induction of mitogenesis, the induction of differentiation, or the inhibition of cell division of responsive cells. A fusion protein or peptide of the invention is considered to be biologically active if it exhibits one or more biological activities of its therapeutic protein's native counterpart.

-continued

<400> SEQUENCE: 66

His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Gly
1			5						10				15		
Gln	Ala	Ala	Lys	Glu	Phe	Ile	Ala	Trp	Leu	Val	Lys	Gly	Arg	Gly	
		20						25					30		

We claim:

1. A fusion protein comprising a modified transferrin (Tf) protein fused to a therapeutic protein or peptide, wherein the Tf protein exhibits reduced glycosylation, reduced metal binding, or reduced receptor binding.

2. A fusion protein of claim 1, wherein the therapeutic protein or peptide is selected from the group comprising β -interferon (IFN), glucagon-like peptide (GLP-1), erythropoietin mimetic peptide (EMP1), T-20, and soluble toxin receptor.

3. A fusion protein of claim 2, wherein the soluble toxin receptor is synaptotagmin I.

4. A fusion protein of claim 1, wherein the therapeutic protein or peptide or the soluble toxin receptor is fused to the C-Terminal end of Tf.

5. A fusion protein of claim 1, wherein the therapeutic protein or peptide or the soluble toxin receptor is fused to the N-terminal end of Tf.

6. A fusion protein of claim 1, wherein the therapeutic protein or peptide or the soluble toxin receptor is inserted into at least one loop of the Tf.

7. A fusion protein of claim 1, wherein the Tf protein has reduced affinity for a transferrin receptor (TfR).

8. A fusion protein of claim 1, wherein the Tf protein is lactoferrin.

9. A fusion protein of claim 7, wherein the Tf protein does not bind a TfR.

10. A fusion protein of claim 1, wherein the Tf protein has reduced affinity for iron.

11. A fusion protein of claim 10, wherein the Tf protein does not bind iron.

12. A fusion protein of claim 1, wherein said Tf protein comprises at least one mutation that prevents glycosylation.

13. A fusion protein of claim 12, wherein the Tf protein is lactoferrin.

14. A fusion protein of claim 1, which is expressed in the presence of tunicamycin.

15. A fusion protein of claim 1, wherein said Tf protein comprises a portion of the N domain of a Tf protein, a bridging peptide and a portion of the C domain of a Tf protein.

16. A fusion protein of claim 15, wherein the bridging peptide links the therapeutic protein or peptide to Tf.

17. A fusion protein of claim 15, wherein the therapeutic protein or peptide is inserted between an N and a C domain of Tf protein.

18. A fusion protein of claim 1, wherein the Tf protein comprises at least one amino acid substitution, deletion or addition in the hinge region.

19. A fusion protein of claim 18, wherein said hinge region is selected from the group consisting of about residue 94 to about residue 96, about residue 245 to about residue 247, about residue 316 to about residue 318, about residue

425 to about residue 427, about residue 581 to about residue 582 and about residue 652 to about residue 658.

20. A fusion protein of claim 1, wherein said Tf protein has at least one amino acid substitution, deletion or addition at a position selected from the group consisting of Asp 63, Gly 65, Tyr 95, Tyr 188, Lys 206, His 207, His 249, Asp 392, Tyr 426, Tyr 514, Tyr 517, His 585, Thr 120, Arg 124, Ala 126, Gly 127, Thr 452, Arg 456, Ala 458 and Gly 459.

21. A fusion protein of claim 6, wherein the therapeutic protein or peptide replaces at least one loop of Tf.

22. A fusion protein of claim 12, wherein the glycosylation site is selected from the group consisting of an amino acid residue corresponding to amino acids N413, N611.

23. A fusion protein of claim 7 or 9, wherein the Tf comprises at least one amino acid substitution, deletion or addition at an amino acid residue corresponding to an amino acid selected from the group consisting of Asp 63, Gly 65, Tyr 95, Tyr 188, Lys 206, His 207, His 249, Asp 392, Tyr 426, Tyr 514, Tyr 517, His 585, Thr 120, Arg 124, Ala 126, Gly 127, Thr 452, Arg 456, Ala 458 and Gly 459.

24. A fusion protein of claim 4, wherein the Tf C-terminal proline residue is deleted.

25. A fusion protein of claim 4, wherein the Tf C-terminal cysteine loop is deleted.

26. A fusion protein of claim 1, wherein the serum half-life of the therapeutic protein or peptide is increased over the serum half-life of the therapeutic protein or peptide or soluble toxin receptor in an unfused state.

27. A fusion protein of claim 1, wherein the Tf protein does not bind a TfR.

28. A fusion protein of claim 1, wherein said Tf protein exhibits reduced or no glycosylation.

29. A fusion protein of claim 28, comprising at least one mutation that prevents glycosylation.

30. A nucleic acid molecule encoding a fusion protein of either claim 1.

31. A vector comprising a nucleic acid molecule of claim 30.

32. A host cell comprising a vector of claim 31.

33. A host cell comprising a nucleic acid molecule of claim 30.

34. A method of expressing a Tf fusion protein comprising culturing a host cell of claim 32 under conditions which express the encoded fusion protein.

35. A method of expressing a Tf fusion protein comprising culturing a host cell of claim 33 under conditions which express the encoded fusion protein.

36. A host cell of claim 32, wherein the cell is prokaryotic or eukaryotic.

37. A host cell of claim 33, wherein the cell is prokaryotic or eukaryotic.

38. A host cell of claim 36, wherein the cell is a yeast cell.

39. A host cell of claim 37, wherein the cell is a yeast cell.

40. A transgenic animal comprising a nucleic acid molecule of 30.

41. A method of producing a Tf fusion protein comprising isolating a fusion protein from a transgenic animal of claim 40.

42. A method of claim 41, wherein the Tf fusion protein comprises lactoferrin.

43. A method of claim 42, wherein the fusion protein is isolated from a biological fluid from the transgenic animal.

44. A method of claim 42, wherein the fluid is serum or milk.

45. A method of treating a disease or disease symptom in a patient, comprising the step of administering a fusion protein of claim 1.

46. The fusion protein of claim 1, wherein the Tf protein has a N-terminal domain at each end of the protein.

47. The fusion protein of claim 46, wherein the therapeutic protein or peptide or the soluble toxin receptor is fused to each N-terminal domain of the Tf protein.

48. The fusion protein of claim 2, wherein the soluble toxin receptor binds specifically to a toxin.

49. A fusion protein of claim 2, wherein the therapeutic protein or peptide is an analog of β -IFN, GLP-1, erythropoietin mimetic peptide (EMP1), T-20, or soluble toxin receptor wherein the analog is effective in treating, preventing, or ameliorating a disease, condition or disorder.

50. A pharmaceutical composition comprising the fusion protein of claims 1, 2 or 3, and a carrier.

51. A method of treating a subject comprising administering to the subject a therapeutically effective amount of a fusion protein of claim 1.

52. A method of claim 51, wherein the subject is suffering from multiple sclerosis, brain tumor, skin cancer, hepatitis B, or hepatitis C, and wherein the fusion protein comprises IFN or an analog thereof.

53. A method of claim 52, wherein the subject is suffering from multiple sclerosis.

54. A method of claim 51, wherein the subject is suffering from elevated level of glucose as compared to a healthy subject and wherein the fusion protein comprises GLP-1 or an analog thereof.

55. A method of claim 54, wherein the elevated level of glucose is associated with diabetes.

56. A method of claim 55, wherein the diabetes is Type II diabetes.

57. A method of claim 51, wherein the subject is suffering from low or defective red blood cell production as compared to a healthy subject and wherein the fusion protein comprises EMP1 or an analog thereof.

58. A method of claim 57, wherein the low or defective red blood cell production is associated with anemia, thalassemia, pregnancy or menstrual disorders, rheumatoid arthritis, AIDS, and cancer.

59. A method of claim 51, wherein the subject is suffering from a disease caused by the transmission of a retrovirus and wherein the therapeutic peptide is an inhibitor of virus entry.

60. A method of claim 59, wherein the retrovirus is a human retrovirus.

61. A method of claim 60, wherein the human retrovirus is selected from the group consisting of HIV-1, HIV-2, and the human T-lymphocyte virus I (HTLV-1), HTLV-II, and HTLV-III.

62. A method of claim 59, wherein the retrovirus is a non-human retrovirus.

63. A method of claim 62, wherein the non-human retrovirus is selected from the group consisting of bovine leukemia virus, feline sarcoma and leukemia viruses, simian sarcoma and leukemia viruses, and sheep progress pneumonia viruses.

64. A method of claim 59, wherein the inhibitor is T-20, T-1249 or an analog thereof.

65. A method of claim 59, wherein the disease is AIDS.

66. A method of preventing or treating a disease or condition associated with a toxin comprising administering to the subject a therapeutically effective amount of a fusion protein comprising a modified Tf protein fused to a soluble toxin receptor, wherein the modified Tf protein exhibits reduced glycosylation, reduced metal binding, or reduced receptor binding.

67. A method of claim 66, wherein the soluble toxin receptor is selected from the group consisting of anthrax toxin receptor, botulinum toxin receptor, and diphtheria toxin receptor.

68. A method of claim 67, wherein the soluble botulinum toxin receptor is amino acids 1-53 (SEQ ID NO: 4) of synaptotagmin.

69. A fusion protein of claim 1, wherein a therapeutic protein or peptide is inserted in one or more of the transferrin loops.

70. A fusion protein of claim 69, wherein a therapeutic protein is inserted in each of the 5 transferrin loops.

71. A fusion protein of claim 2, wherein the GLP-1 further comprises an additional amino acid at the N-terminus.

72. The fusion protein of claim 71, wherein the amino acid is Gly.

73. The fusion protein of claim 71, wherein the GLP-1 analog is fused to modified transferrin protein at the N-terminal end.

74. A method of regulating glucose level in a subject comprising administering to the subject a therapeutically effective amount of a fusion protein comprising a modified Tf protein fused to GLP-1 or analog thereof, wherein the modified Tf protein exhibits reduced glycosylation, reduced metal binding, or reduced receptor binding.

75. A fusion protein of claim 1, wherein the therapeutic protein or peptide is inserted into the N-domain of mTf at one or more of the sites selected from the group consisting of Asp33, Asn55, Asn 75, Asp90, Gly257, Lys280, His289, Ser298, Ser105, Glu141, Asp166, Gln184, asp197, Lys217, Thr231, and Cys241.

76. A fusion protein of claim 1, wherein the therapeutic protein or peptide is inserted into the C-domain of mTf at one or more sites corresponding to Asp33, Asn55, Asn 75, Asp90, Gly257, Lys280, His289, Ser298, Ser105, Glu141, Asp166, Gln184, asp197, Lys217, Thr231, or Cys241.

77. A fusion protein of claim 75, wherein the therapeutic protein or peptide is further inserted into the mTf at one or more sites corresponding to Asp33, Asn55, Asn 75, Asp90, Gly257, Lys280, His289, Ser298, Ser105, Glu141, Asp166, Gln184, asp197, Lys217, Thr231, or Cys241.

78. A fusion protein of claim 2, wherein the therapeutic peptide is EMP1 and wherein EMP1 is inserted into the N-domain of mTf at one or more sites selected from the group consisting of His289 and Asp166.

79. A fusion protein of claim 2, wherein the therapeutic peptide is EMP1 and wherein EMP1 is inserted into the C-domain of mTf at one or more sites corresponding to His289 or Asp166.

80. A fusion protein of claim 78, wherein the therapeutic peptide is further inserted into the C-domain of mTf at one or more sites corresponding to His289 or Asp166.

81. A fusion protein of claim 1, wherein mTf is further modified by deletion of the C-terminus Pro.

82. A fusion protein of claim 81, wherein mTf is further modified by deletion of Arg-Arg adjacent to the C-terminus Pro.

83. A fusion protein of claim 1, wherein the mTf is further modified by removing the disulfide bond between Cys402 and Cys674.

84. A fusion protein of claim 83, wherein the disulfide bond is removed by mutating Cys402 and Cys674 into Gly residues.

85. A fusion protein of claim 82, wherein the mTf is further modified by mutating Cys402 and Cys674 into Gly residues.

86. A fusion protein of claim 1, wherein the therapeutic peptide or protein is inserted into one or more of the loops selected from the group consisting of N1(286-292), N₂(162-170), C₁(489-495), and C₂(623-628).

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