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Schellenberger et al.(10) **Pub. No.: US 2010/0189682 A1**(43) **Pub. Date: Jul. 29, 2010**(54) **BIOLOGICALLY ACTIVE PROTEINS
HAVING INCREASED IN VIVO AND/OR IN
VITRO STABILITY****Publication Classification**(76) Inventors: **Volker Schellenberger**, Palo Alto,
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PALO ALTO, CA 94304-1050 (US)(21) Appl. No.: **12/634,556**(22) Filed: **Dec. 9, 2009****Related U.S. Application Data**(63) Continuation of application No. 11/715,276, filed on
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on Sep. 27, 2005, provisional application No. 60/721,
188, filed on Sep. 27, 2005, provisional application
No. 60/743,622, filed on Mar. 21, 2006.(51) **Int. Cl.****A61K 38/20** (2006.01)
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A61P 3/10 (2006.01)
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435/183; 435/320.1; 435/325; 435/69.1

(57)

ABSTRACT

The present invention provides unstructured recombinant polymers (URPs) and proteins containing one or more of the URPs. The present invention also provides microproteins, toxins and other related proteinaceous entities, as well as genetic packages displaying these entities. The present invention also provides recombinant polypeptides including vectors encoding the subject proteinaceous entities, as well as host cells comprising the vectors. The subject compositions have a variety of utilities including a range of pharmaceutical applications.

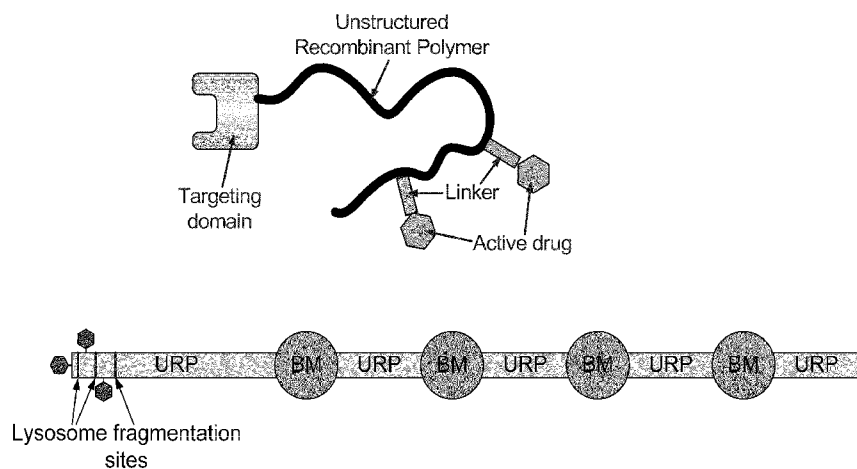
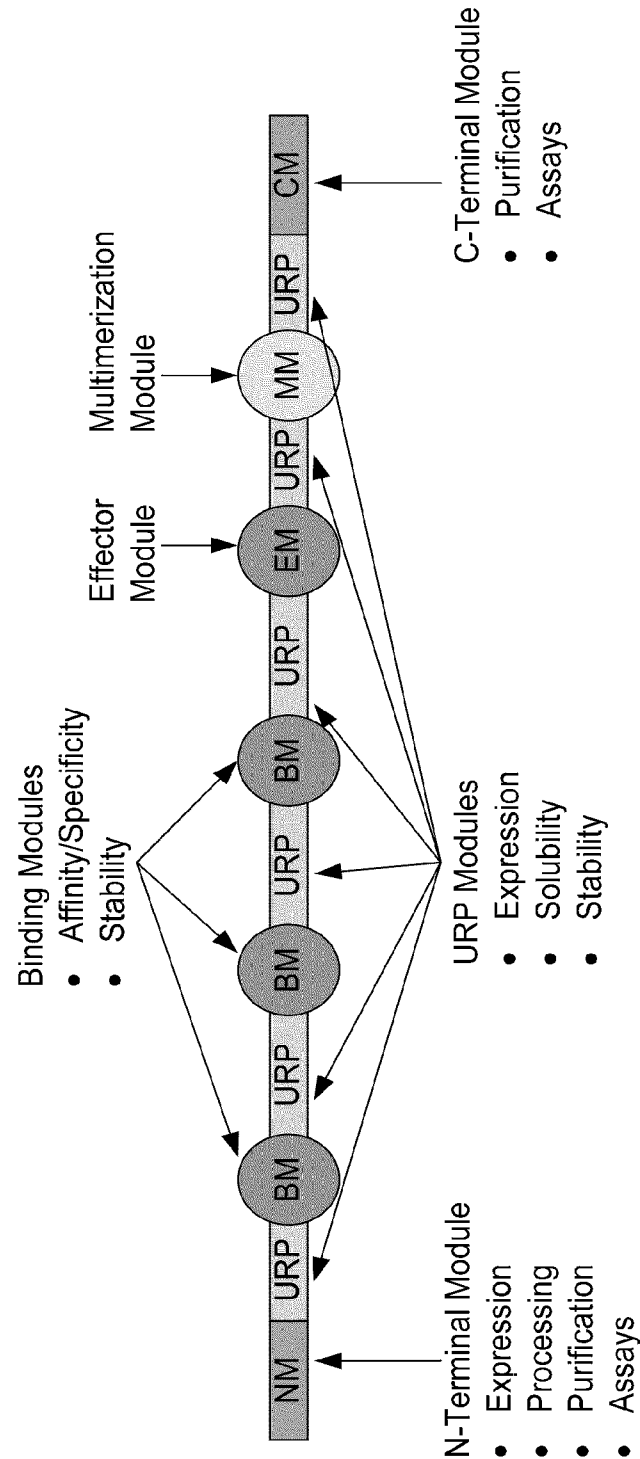
Drug Delivery Constructs

Fig. 1: Multifunctional Unstructured Recombinant Proteins (MURPs)



Binding modules can have the same or different specificity

Fig. 2: Examples of MURPs with few domains

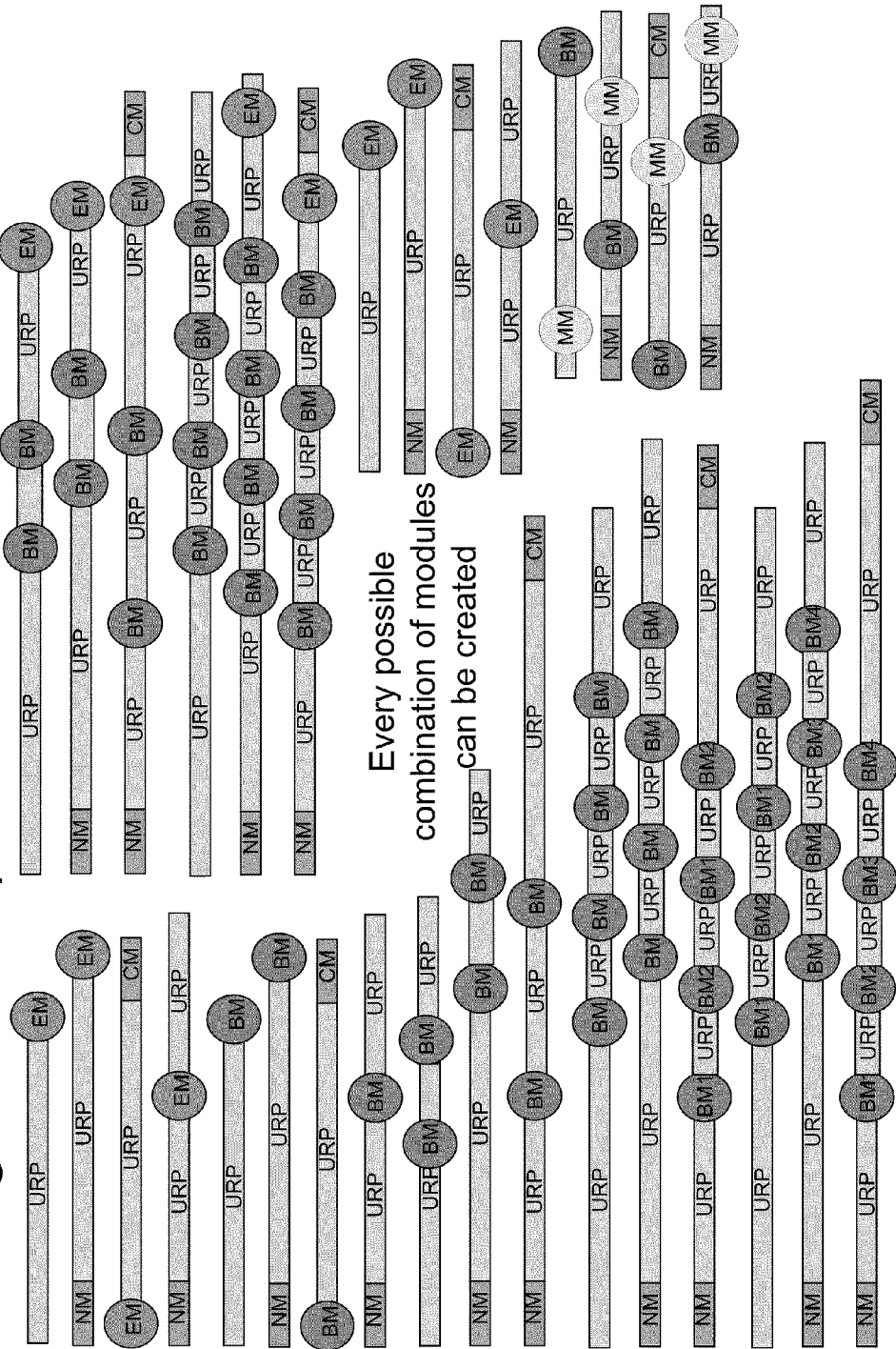


Fig. 3: URP sequences as oligomers of human sequences

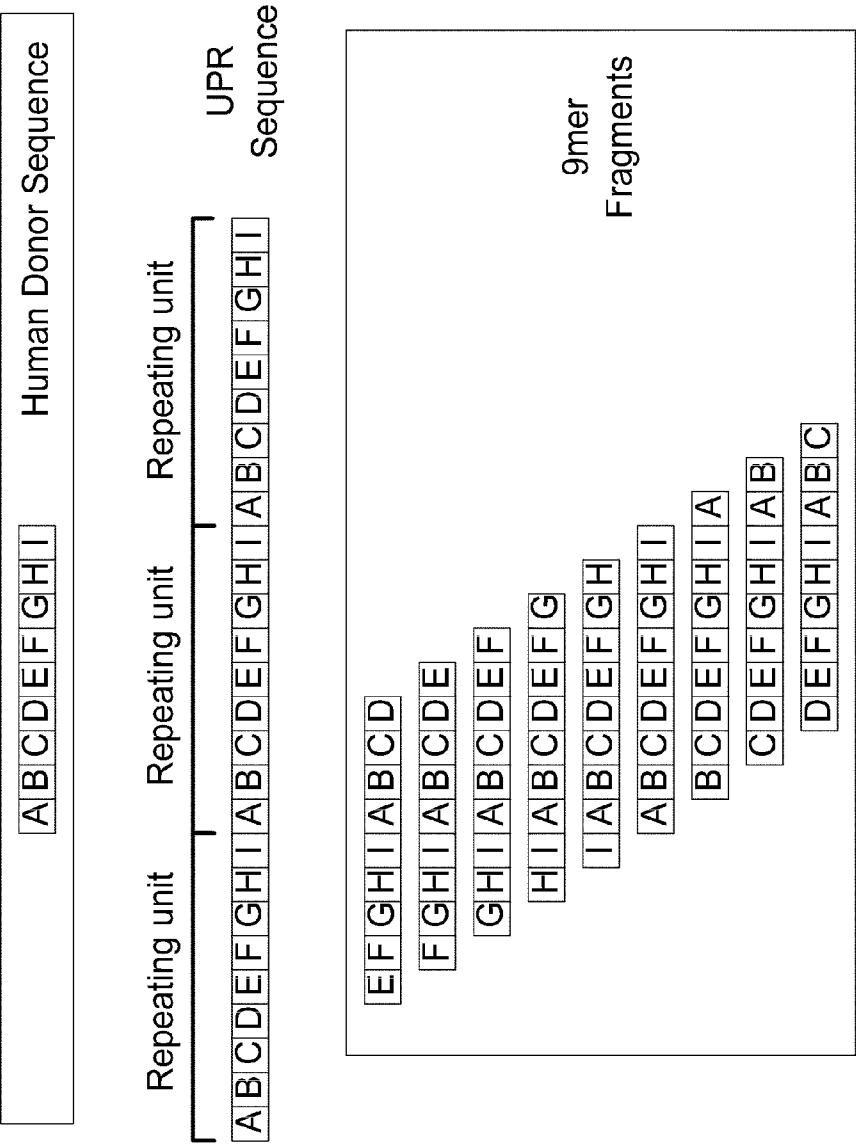


Fig. 4. URP sequences as oligomers of overlapping human sequences

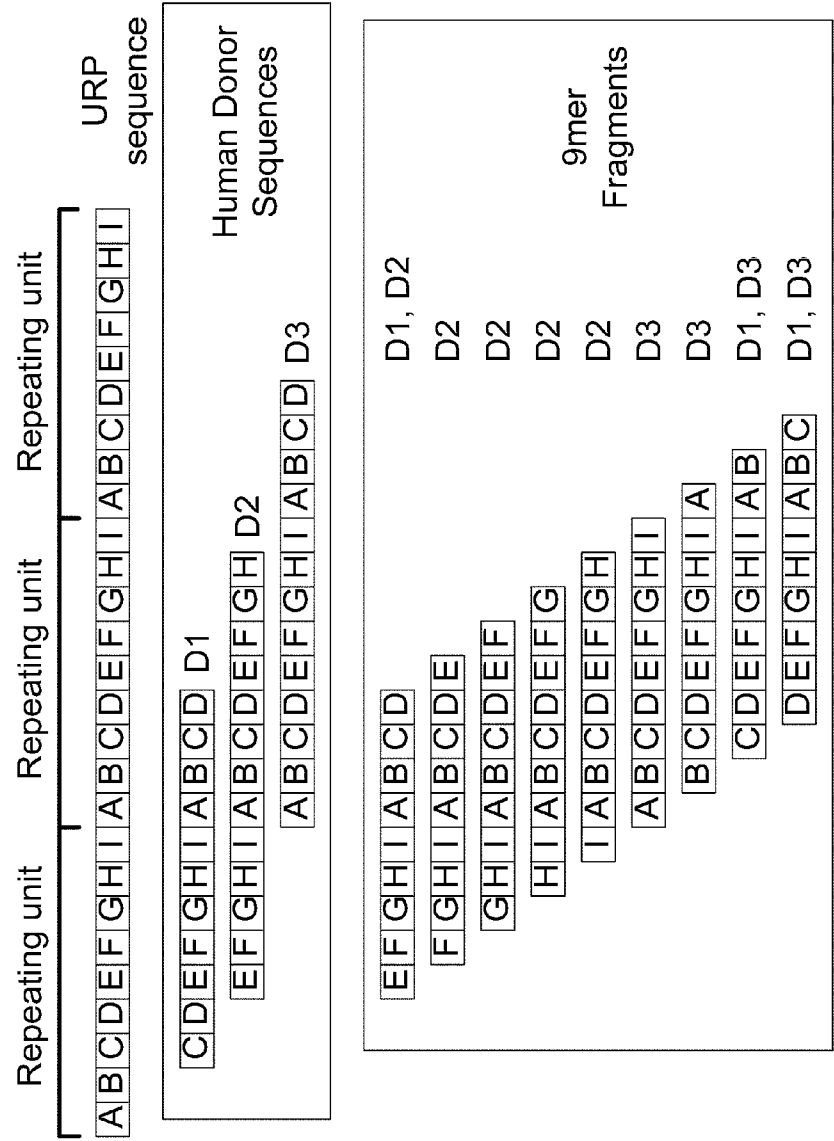


Fig. 5. Glycine/serine-rich URP sequences based on three overlapping human sequences

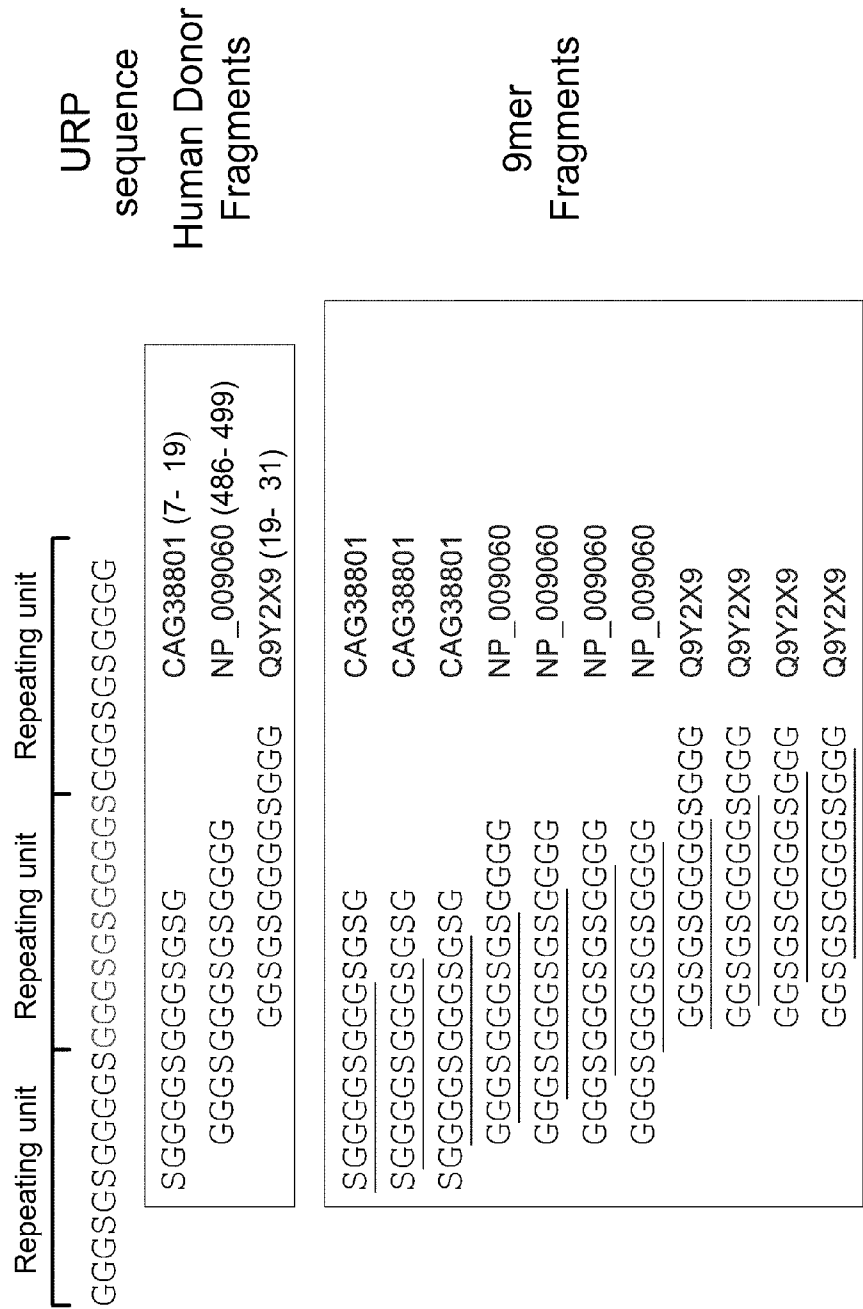


Fig. 7: Interruption of Module-Spanning T cell epitopes by URP Modules

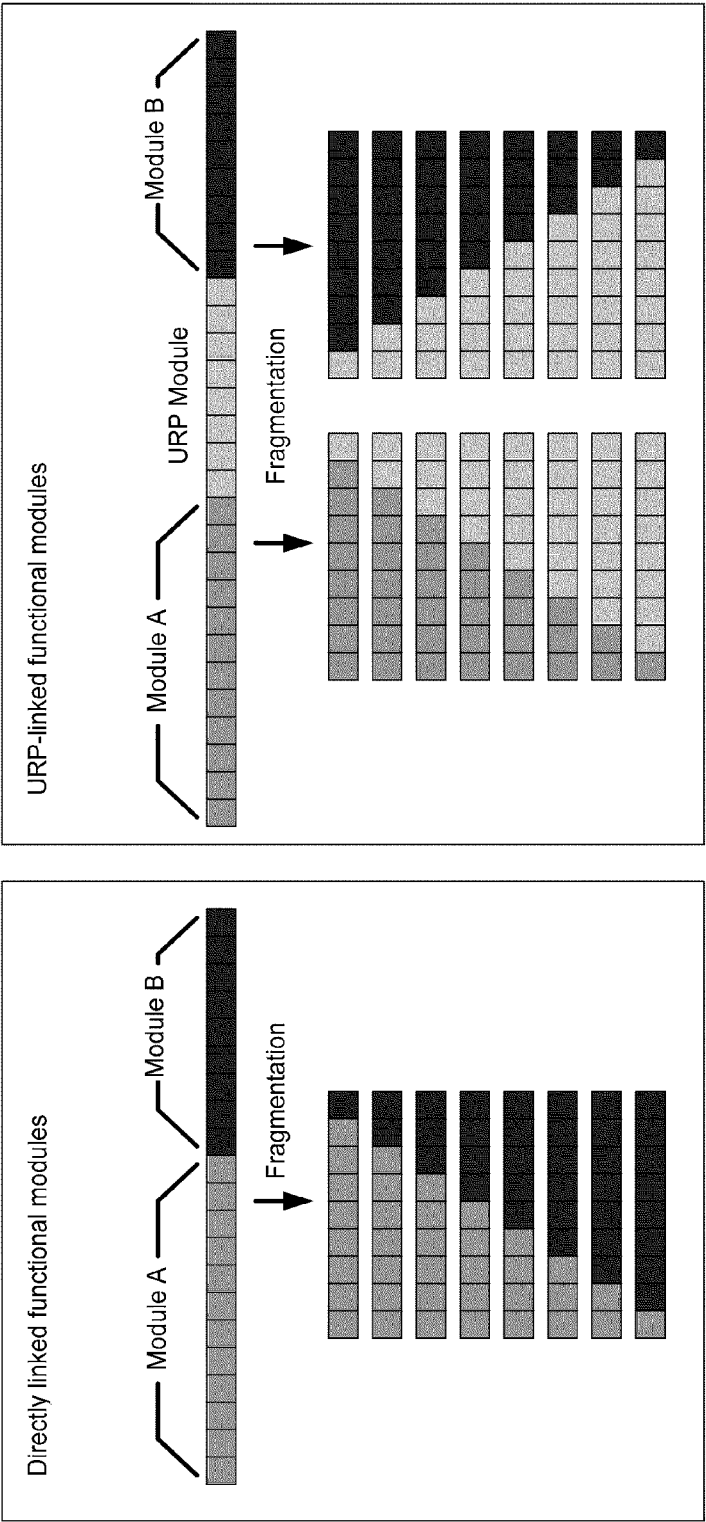


Figure 8. Drug Delivery Constructs

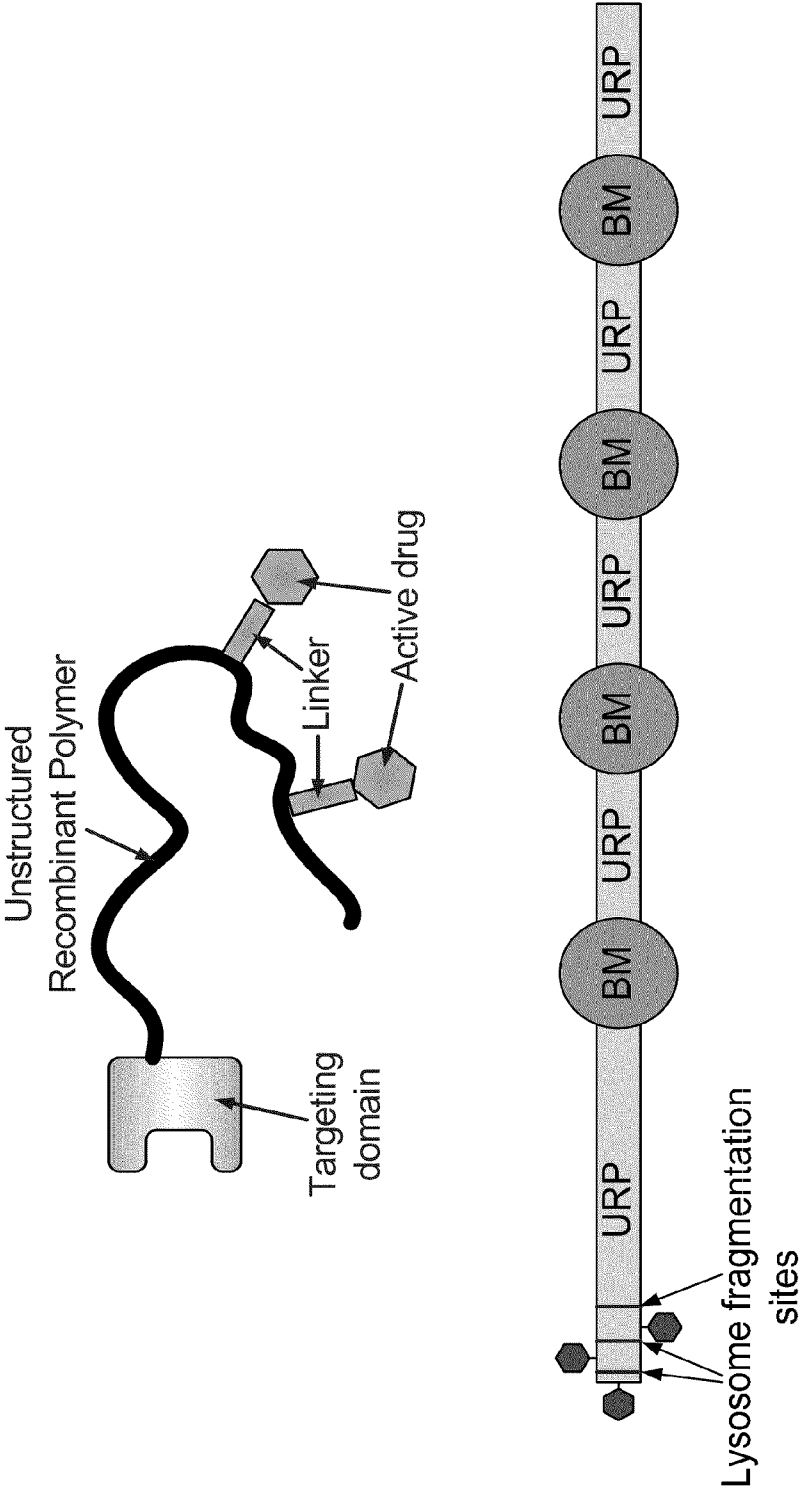


Figure 9. Example of a MURP containing a protease-sensitive site

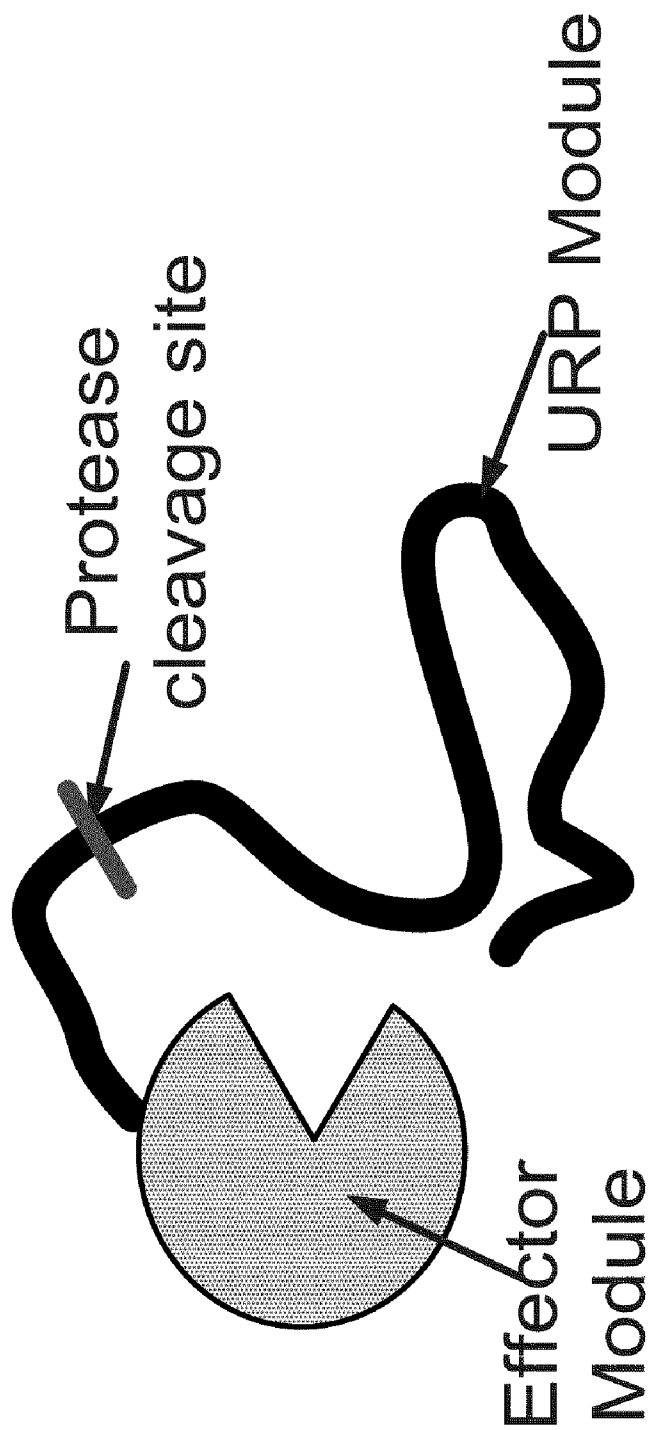


Figure 10. Increasing the local concentration of an effector module

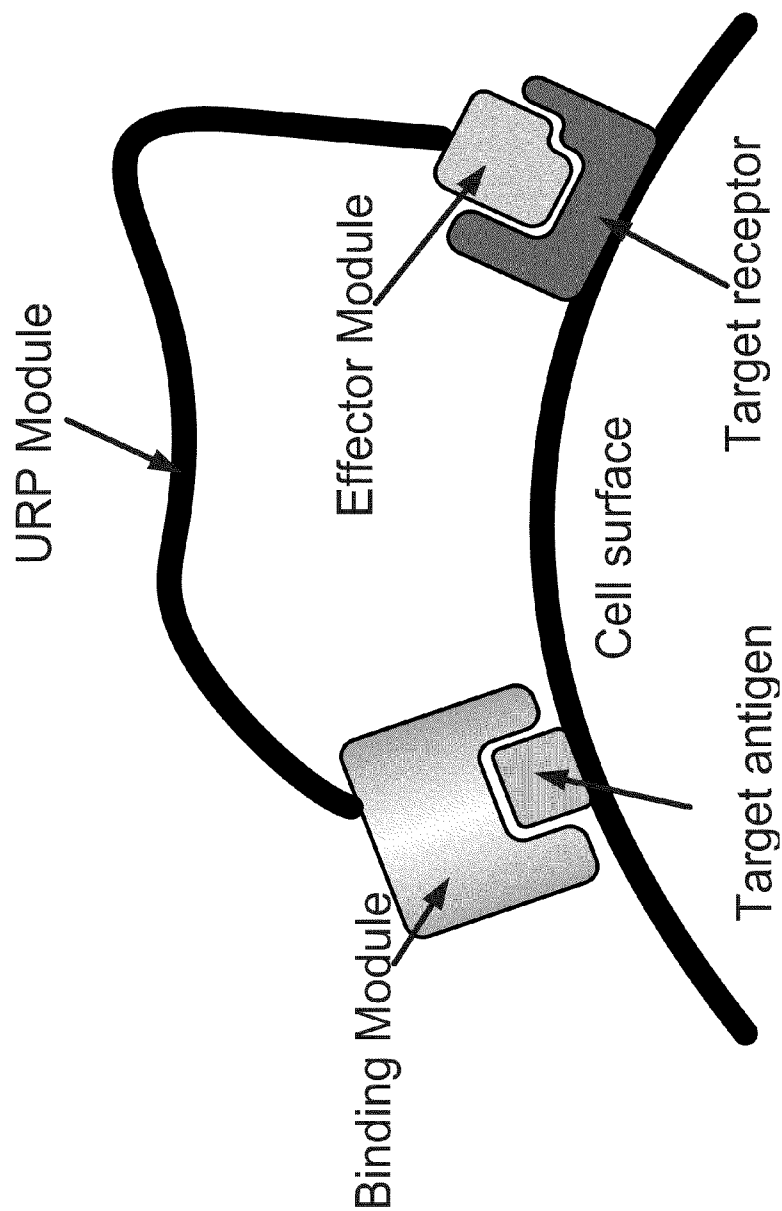


Fig. 11 Construction of URP Modules by iterative dimerization

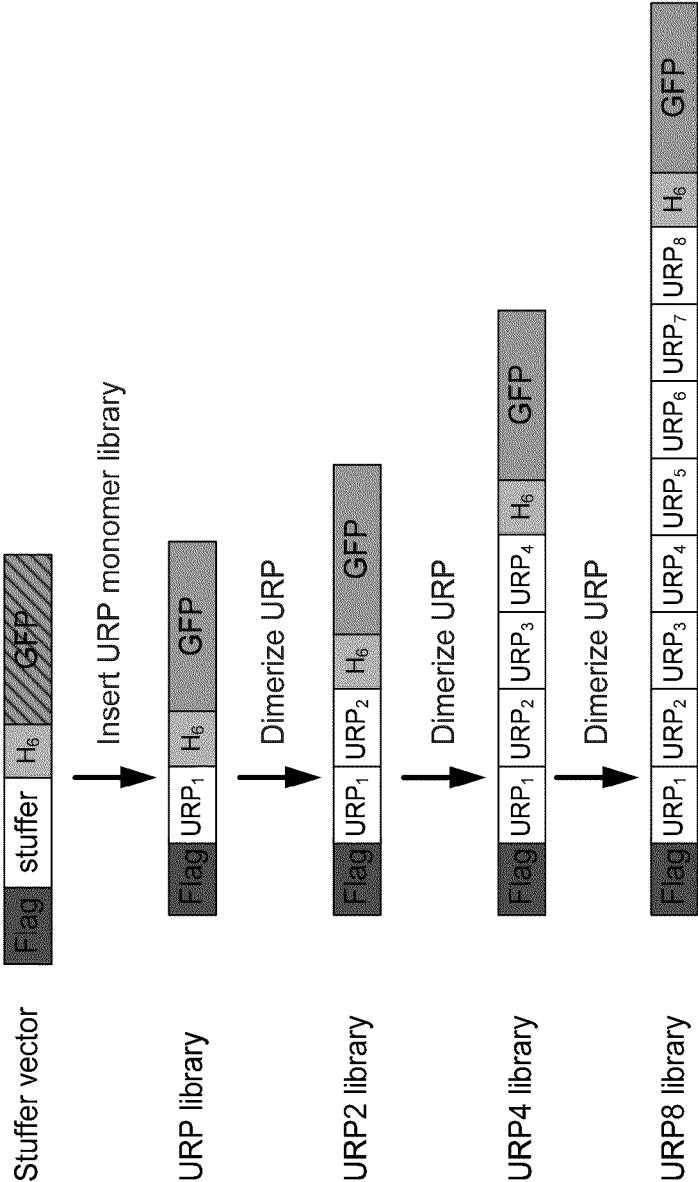


Fig. 12: Examples of MURPs with specificity for death receptors

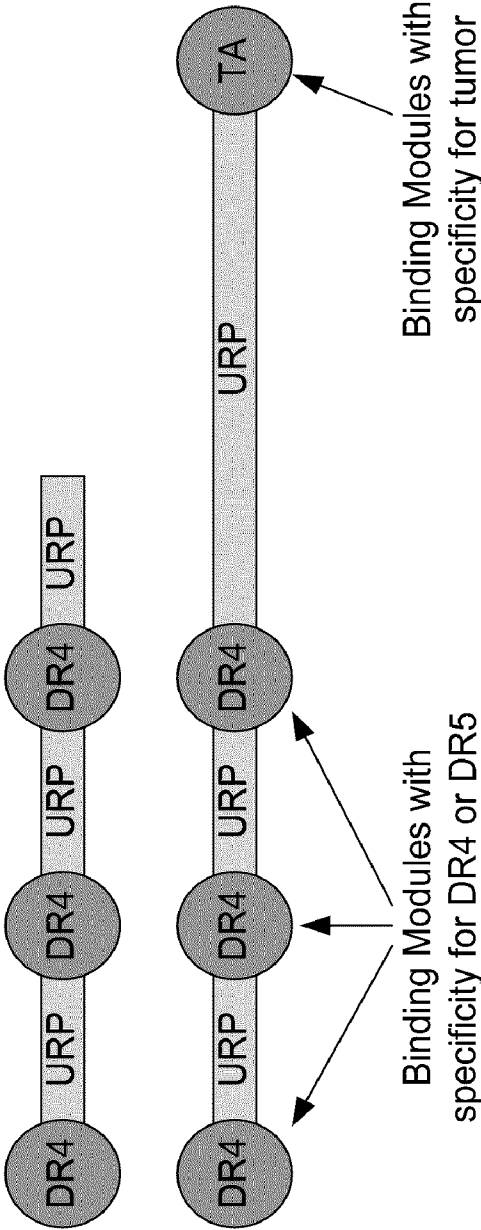


Fig. 13 Tumor antigen-targeted IL2

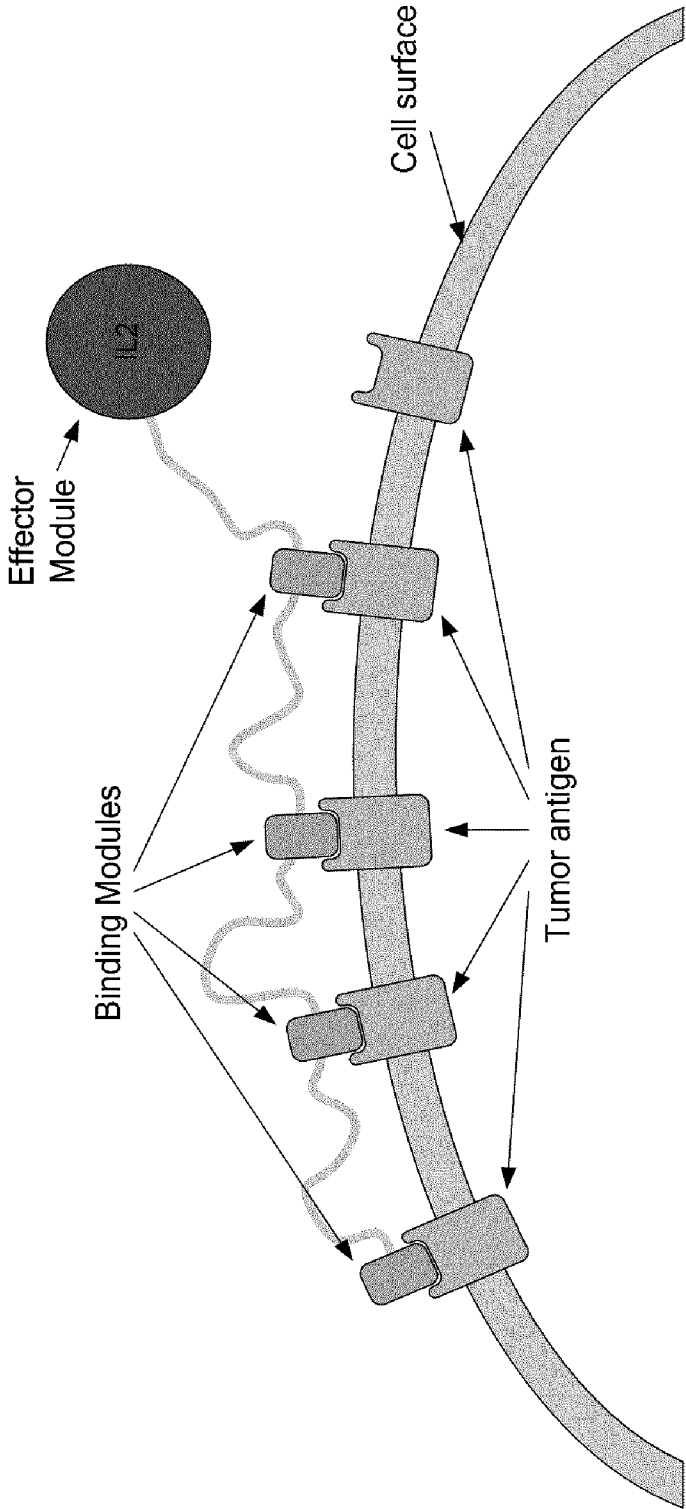


Fig. 14 Construction of rPEG_H288 and rPEG_J288

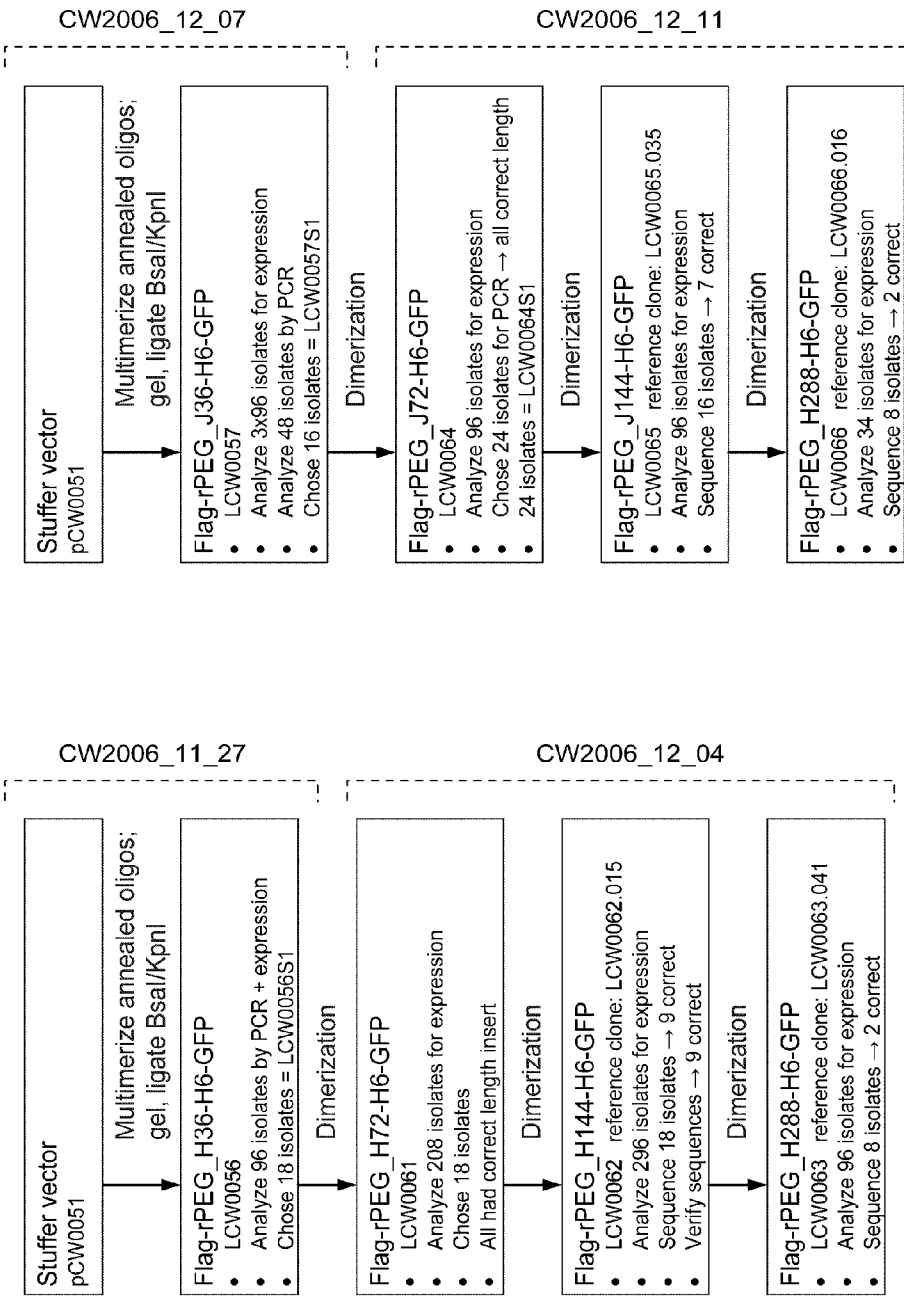


Fig. 15 Sequence of rPEG_J288

G S G G E G G S G G E G G S G G E G G S
GGTAGTGGTGAAGGAGGTTCTGCTGGAGAAAGGAGGTAGTGGAGGTGAAGGTGGATCCGGAGGAGAAGGAGGTAGT
G G E G G S G G E G G S G G E G G S G G E G G S G
GGAGGTGAAGGAGGATCCGGAGGAGAAAGGAGGTAGTGGTGGTGAAGGAGGTTCTGGTGGAGAAAGGAGGTAGTGGAGGT
E G G S G G E G G S G G E G G S G G E G G S G G E G
GAAGGTGGATCCGGAGGAGAGGAGGTAGTGGAGGTGAAGGAGGATCCGGAGGAGAAAGGAGGTAGTGGAGGTGAAGGT
G S G G E G G S G G E G G S G G E G G S G G E G G S
GGATCCGGTGGAGAGGAGGTAGTGGAGGTGAAGGAGGTTCCGGTGGAGAAAGGAGGTAGTGGAGGAGAGGAGGTGGATCT
G G E G G S G G E G G S G G E G G S G G E G G S G
GGAGGAGAAAGGAGGTAGTGGAGGAGAGGGTGGTTCTGGAGGAGAAAGGAGGTAGTGGTGGAGAGGGTGGATCTGGTGGGA
E G G S G G E G G S G G E G G S G G E G G S G G E G
GAAGGAGGTAGTGGAGGAGAAAGGTGGTTCTGGAGGAGAAAGGAGGTAGTGGTGAAGGAGGTTCTGGTGGAGAAAGGA
G S G G E G G S G G E G G S G G E G G S G G E G G S
GGTAGTGGAGGTGAAGGTGGATCCGGAGGAGAAAGGAGGTAGTGGAGGTGAAGGAGGATCCGGAGGAGAAAGGAGGTAGT
G G E G G S G G E G G S G G E G G S G G E G G S G
GGTGGTGAAGGAGGTTCTGGTGGAGAAAGGAGGTAGTGGAGGTGAAGGTGGATCCGGAGGAGAAAGGAGGTAGTGGAGGT
E G G S G G E G G S G G E G G S G G E G G S G G E G
GAAGGAGGATCCGGAGGAGAGGAGGTAGTGGAGGTGAAGGTGGATCCGGTGGAGAAAGGAGGTAGTGGAGGTGAAGGA
G S G G E G G S G G E G G S G G E G G S G G E G G S
GGTCCGGTGGAGAGGAGGTAGTGGAGGAGAGGGTGGATCTGGAGGAGAAAGGAGGTAGTGGAGGAGAGGAGGTGGTTCT
G G E G G S G G E G G S G G E G G S G G E G G S G
GGAGGAGAAAGGAGGTAGTGGTGGAGAGGGTGGATCTGGTGGAGAAAGGAGGTAGTGGAGGAGAAAGGTGGTTCTGGAGGA
E G
GAAGGA

Fig. 16 Sequence of rPEG_H288

[illegible]

Fig. 18 Depot Derivatives of MURPs

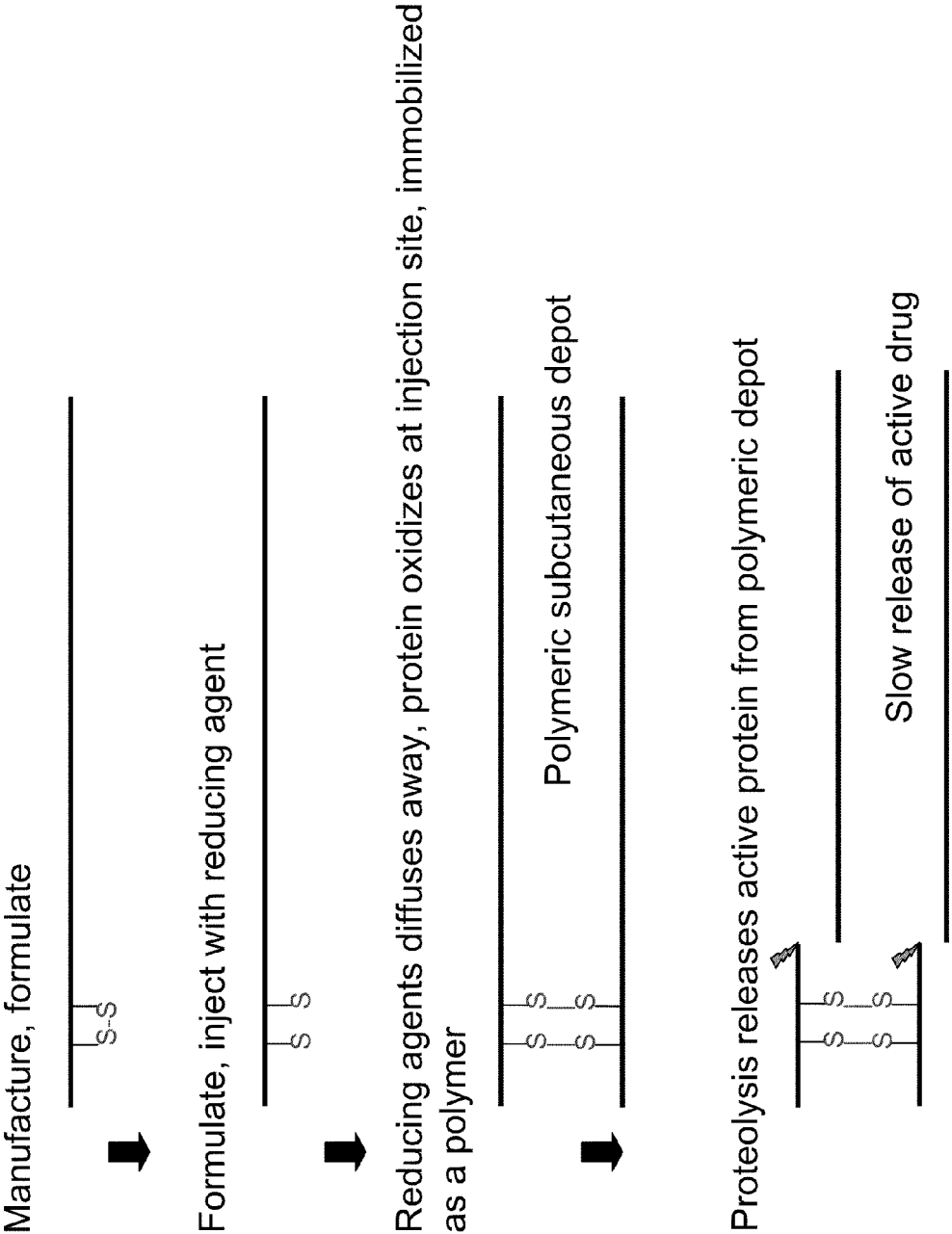
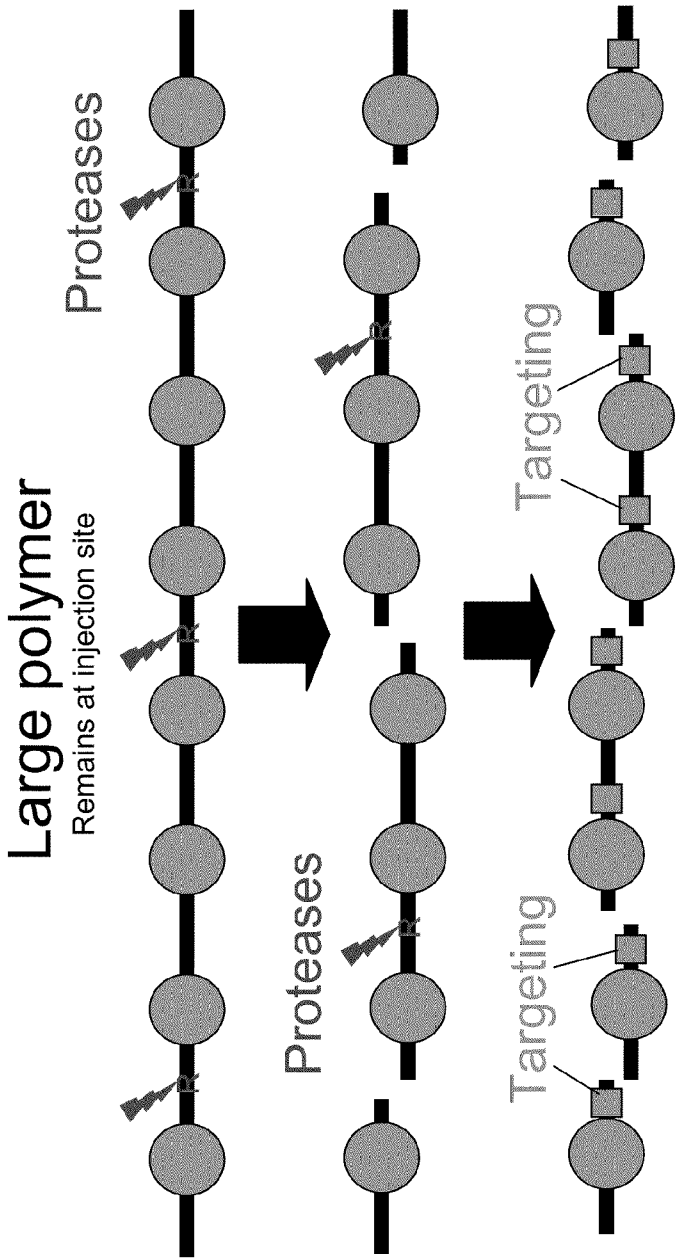
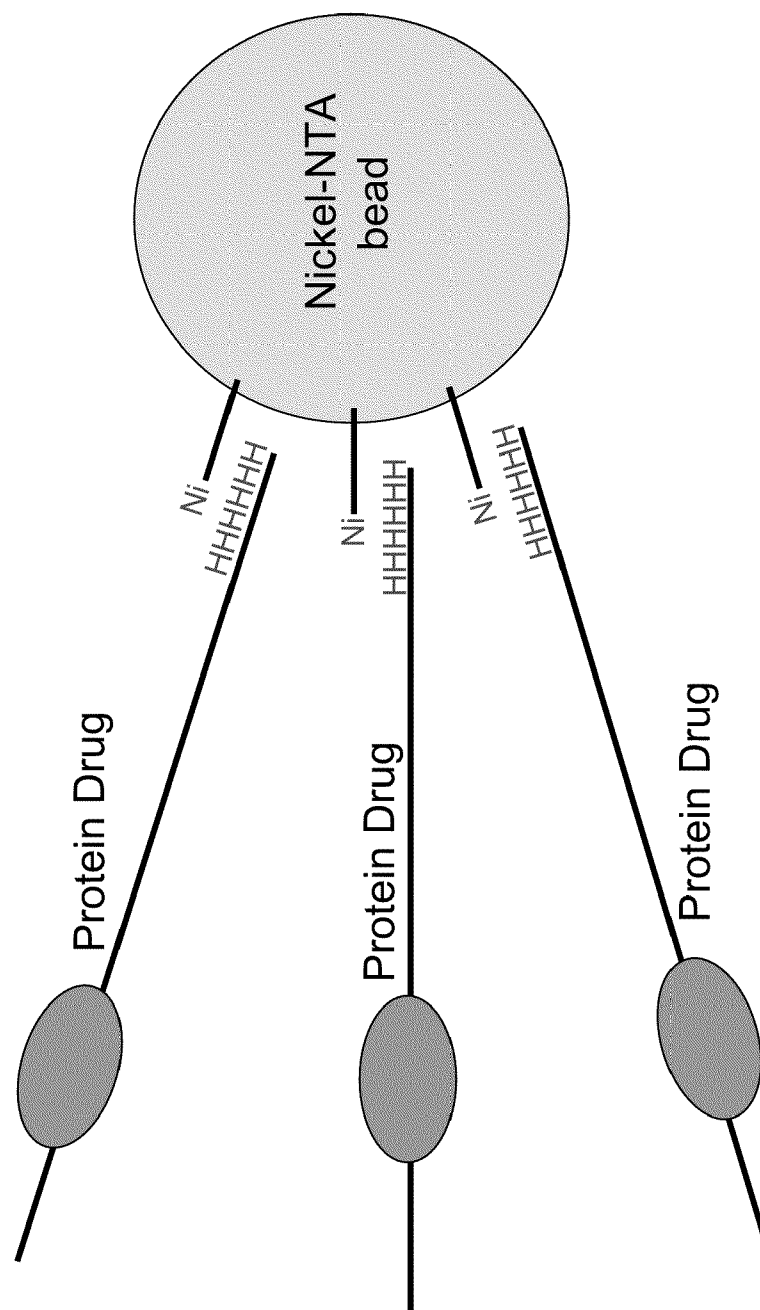


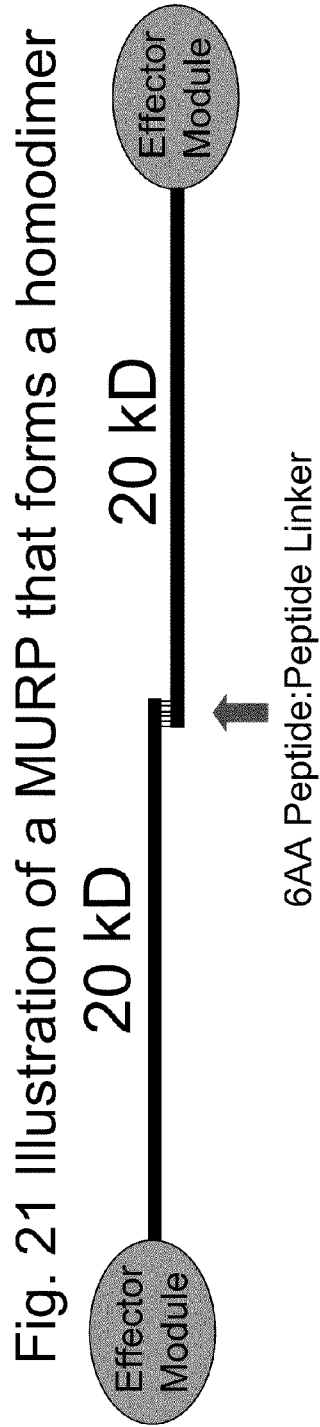
Fig. 19 MURP engineered for slow release



Gradual release of fragments from injection site depot into blood

Fig. 20 Depot Derivatives of MURPs based on His-rich sequences





RADARADA	_____	RADARADA
RARARARA	_____	DADADADA
HAHAHAHA	_____	DADADADA

Preferred, since manufactured as one molecule
which does not polymerize at high pH.
Only at low pH is the H positively charged

RGD is short sequence that binds with good affinity to a very abundant target in serum;
gpIIb/IIIa inhibition is generally safe and in fact preferred; similar to Aspirin.

RGD	RGD	RGD	RGD	RGD
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Fig. 22. Optimizing ion channel blockers

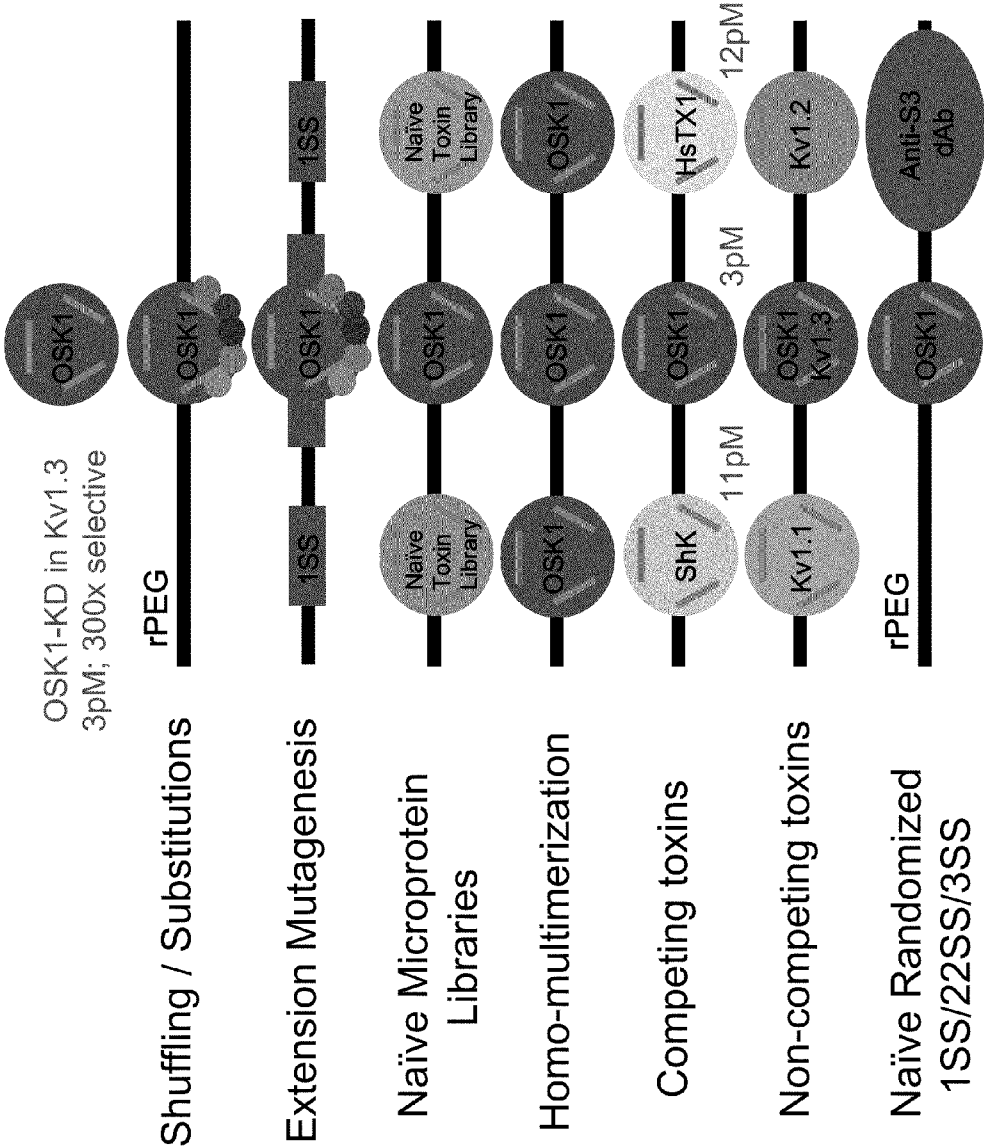
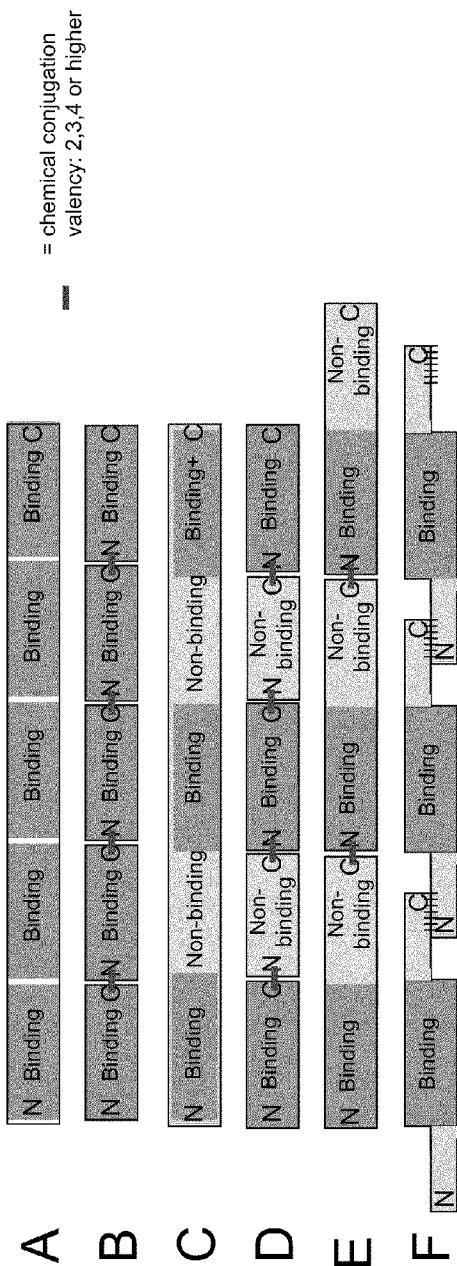
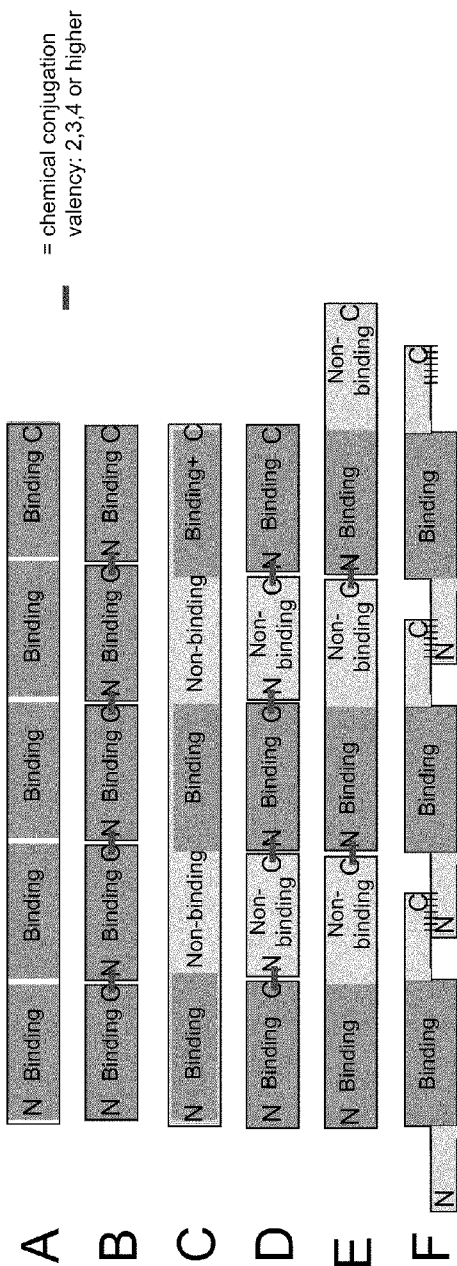
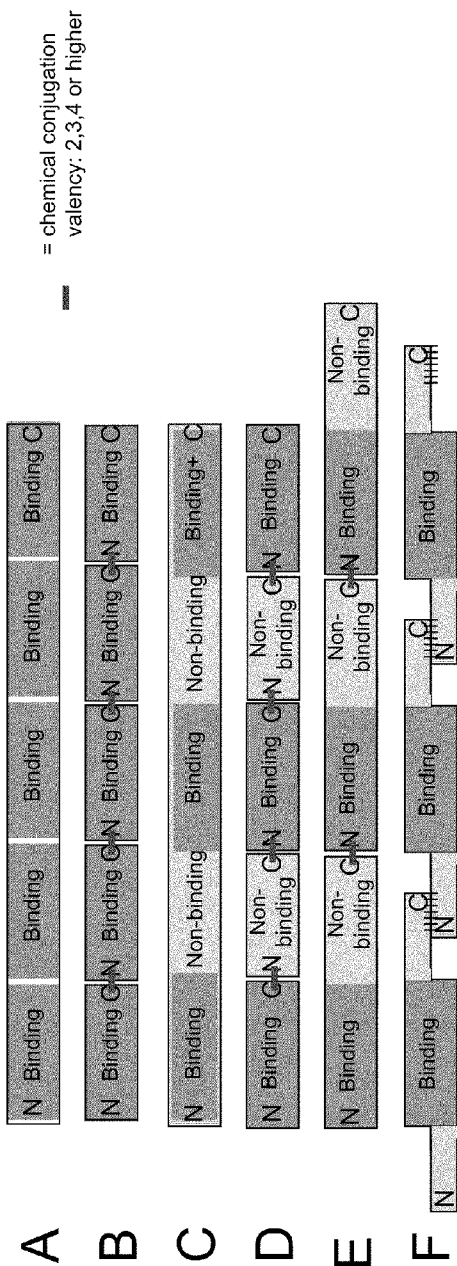
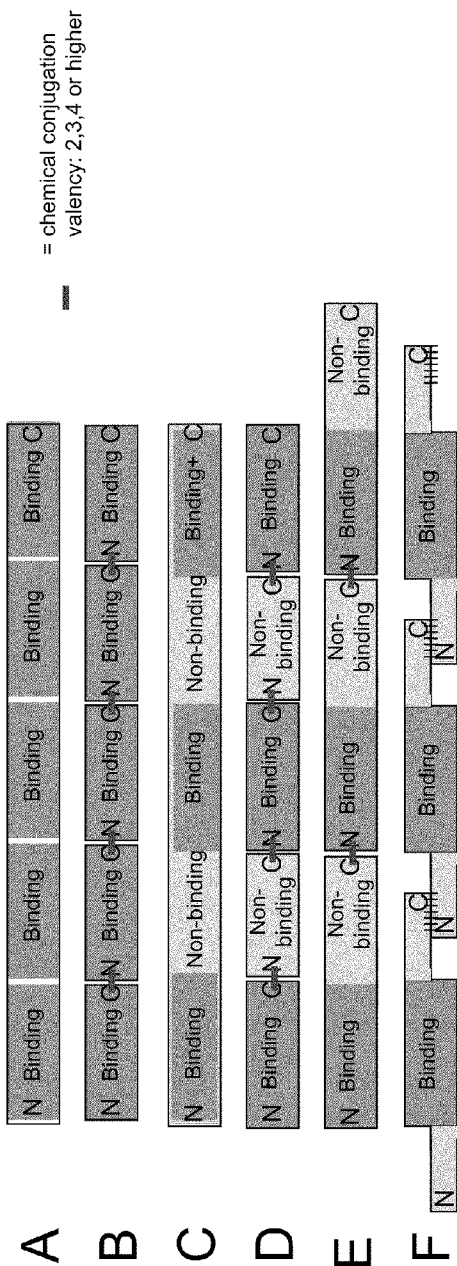
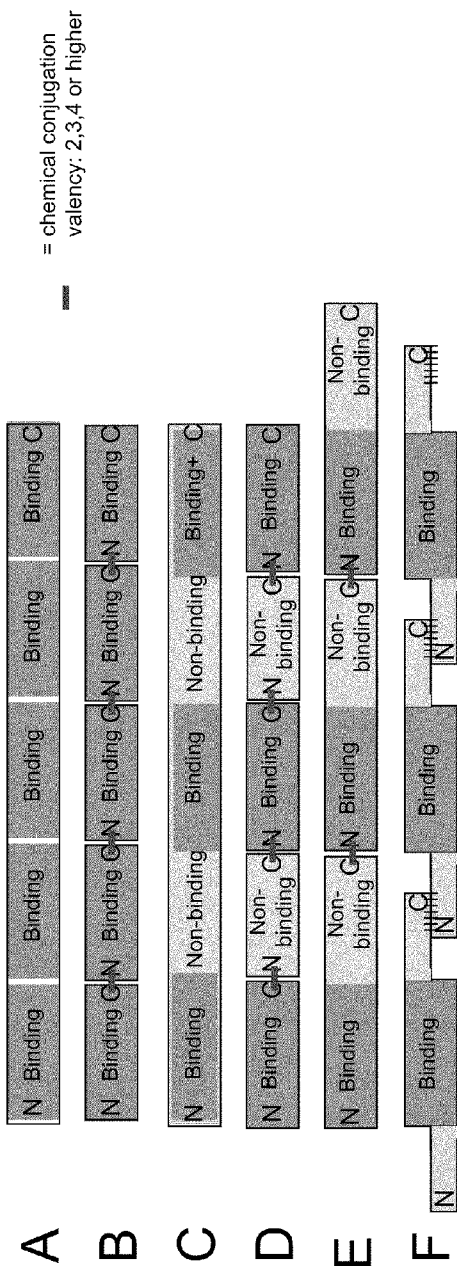
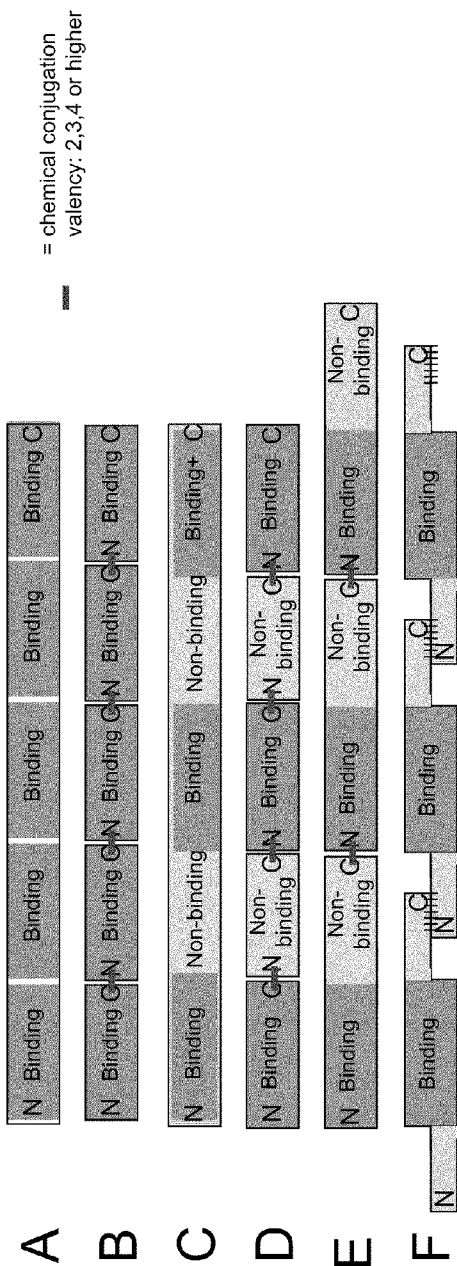


Fig. 23 Additional Half-life Concepts



= chemical conjugation
valency: 2,3,4 or higher

Fig. 24 Universal MURP

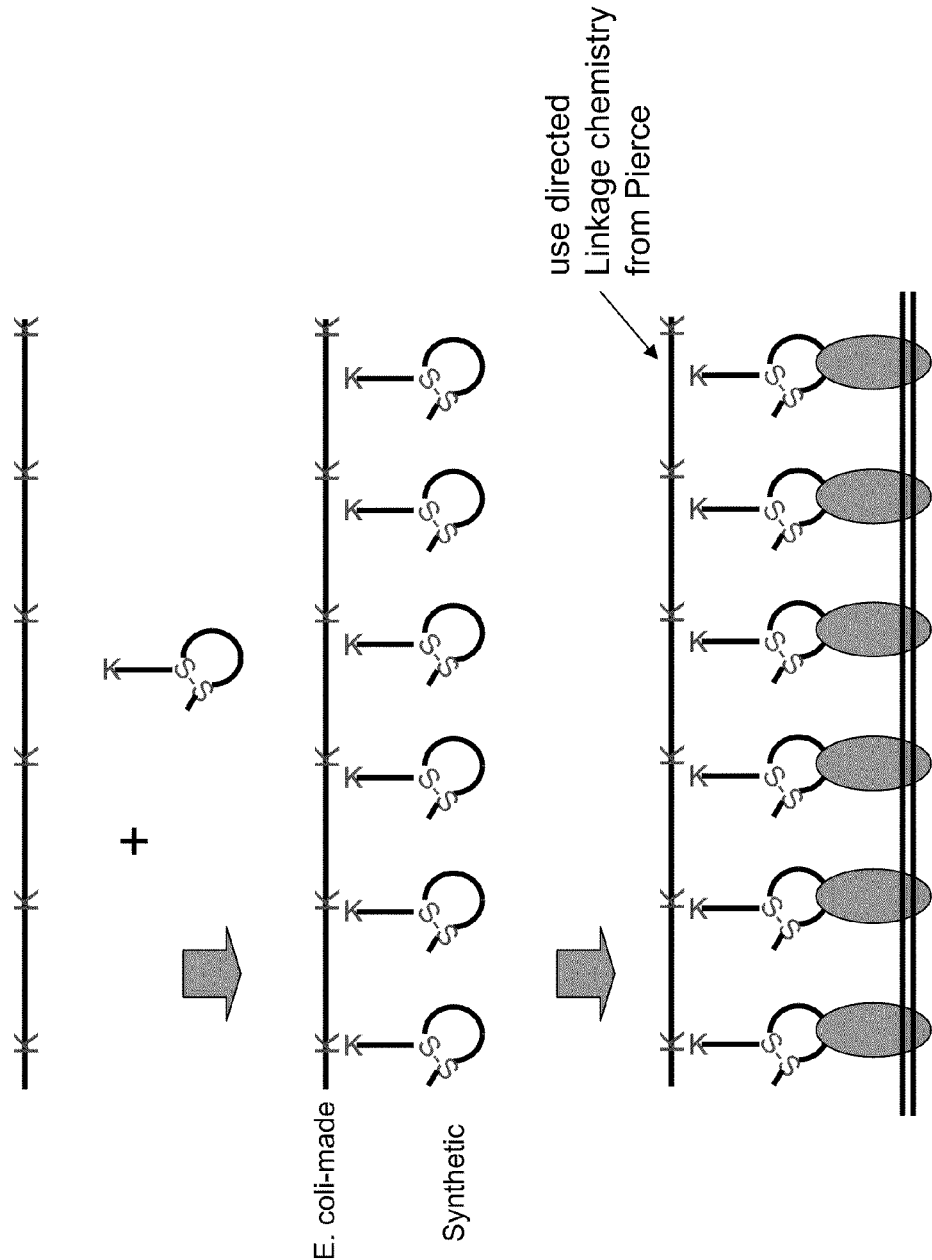


Fig. 25. Buildup of 2SS Binding Modules

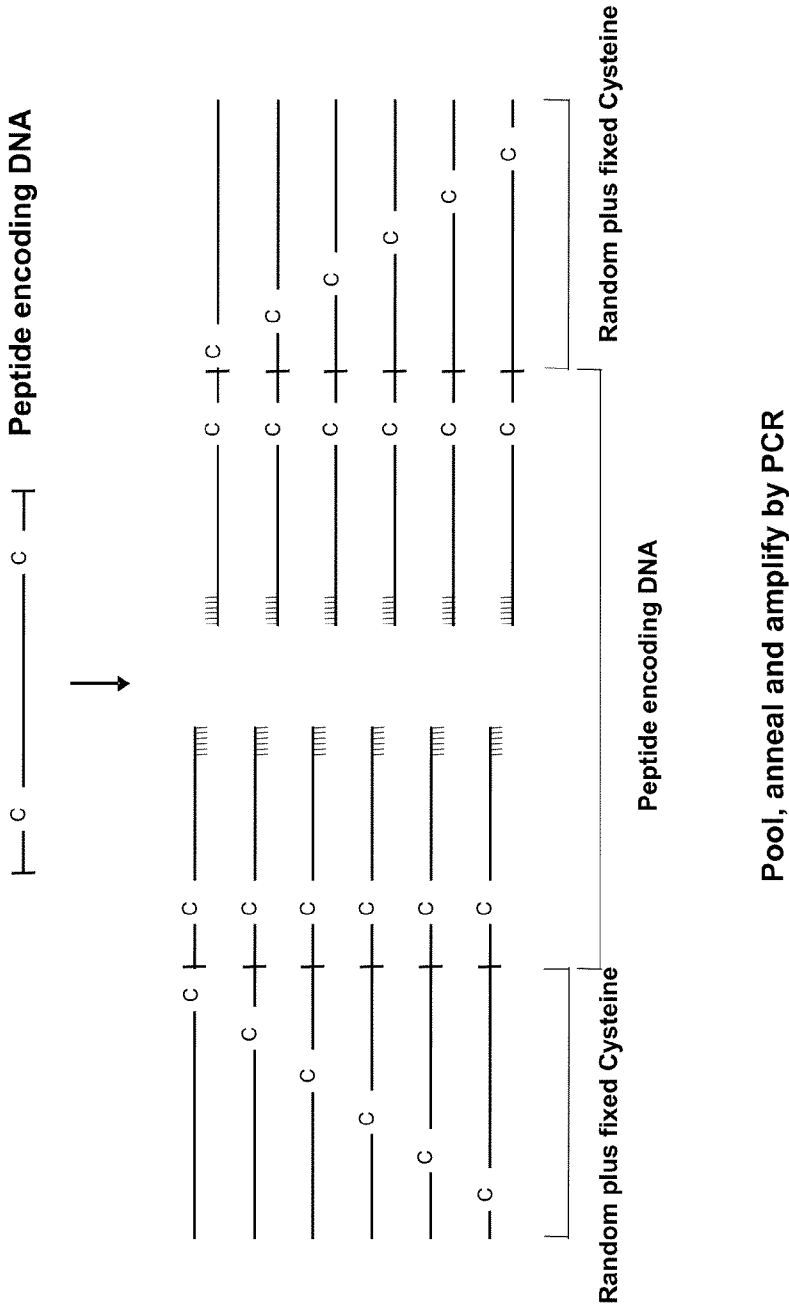


Fig. 28. Plasma stability of rPEG_J288

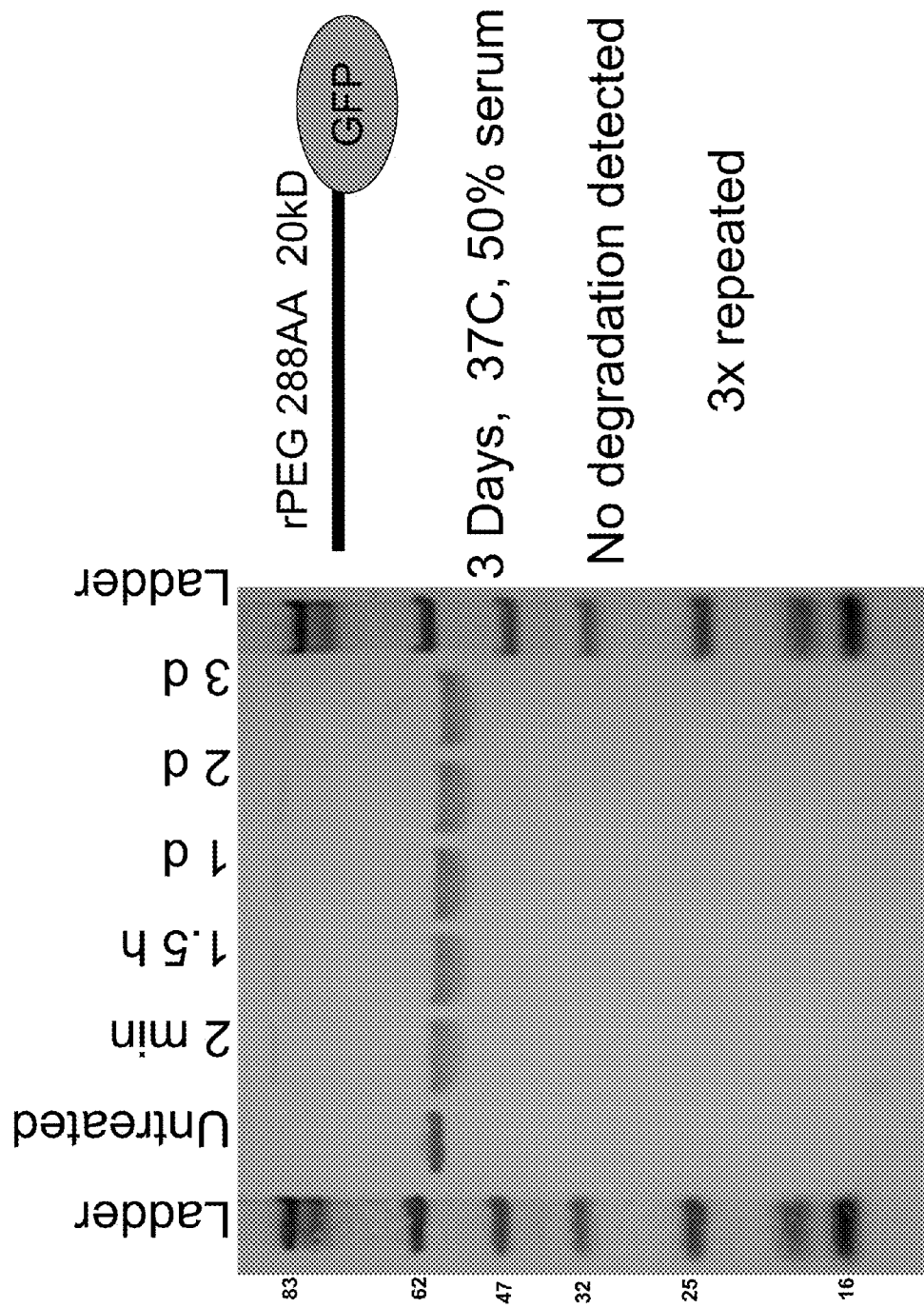


Fig. 29. Absence of pre-existing antibodies against URP

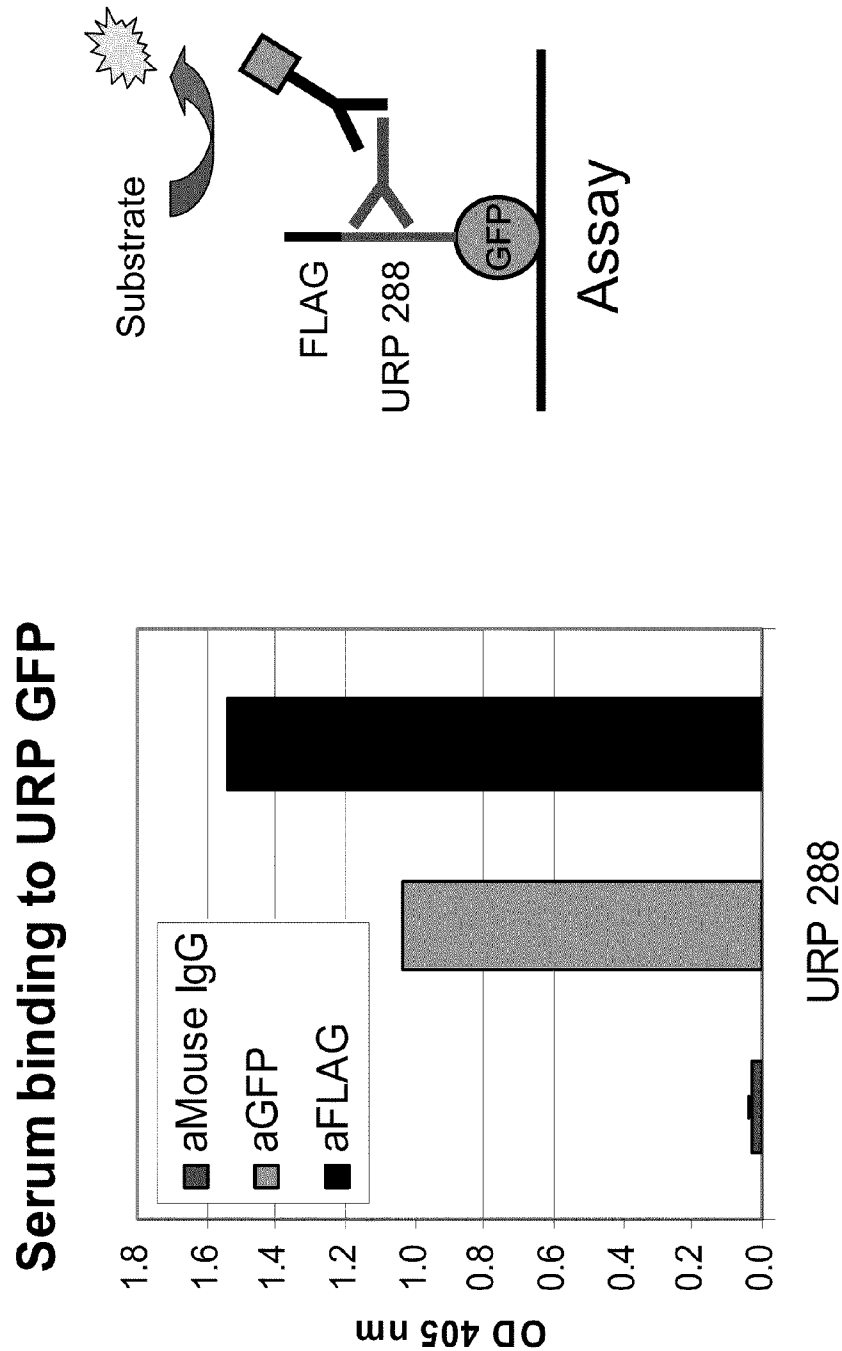


Fig. 30. Binding affinity of anti-VEGF binding modules

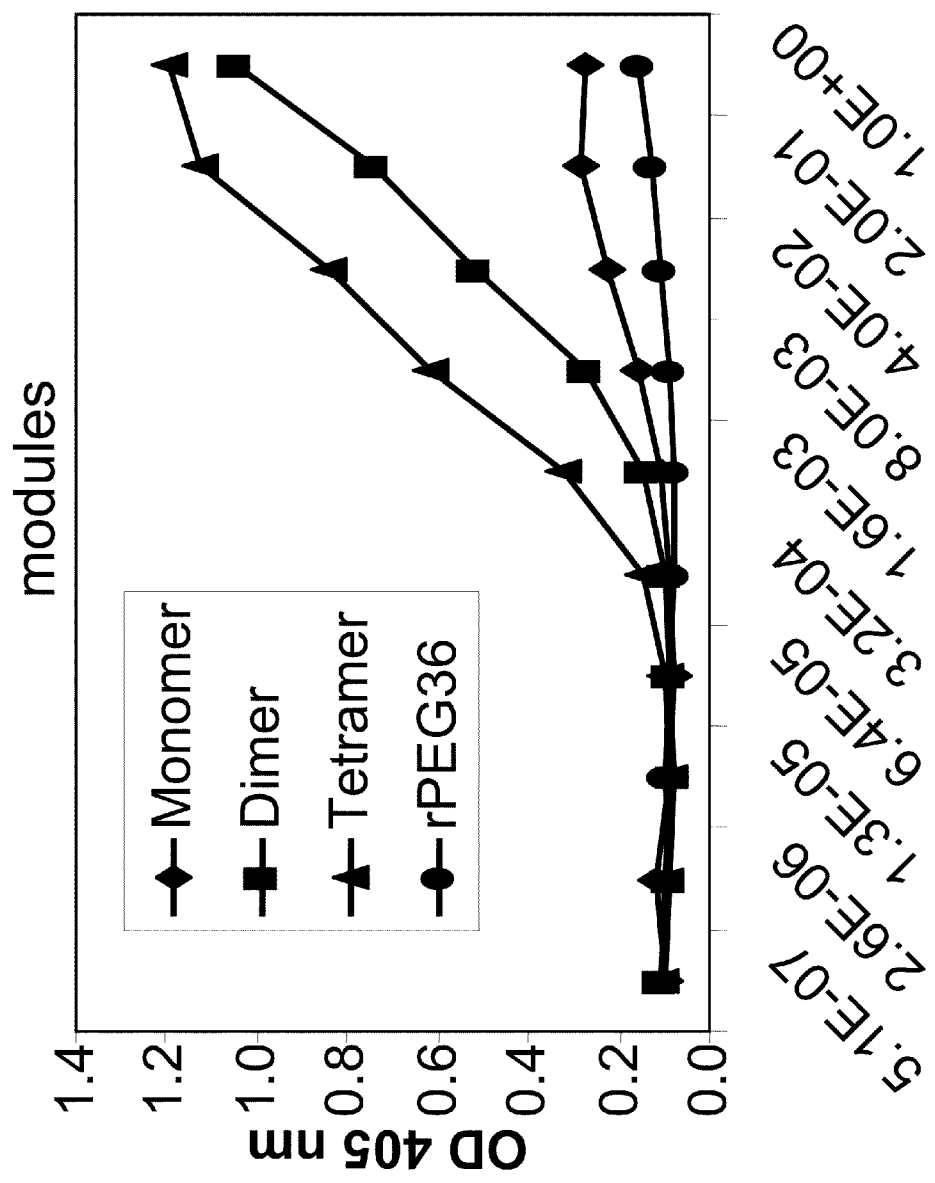


Fig. 31. MURP designed for drug conjugation with specificity for EpCAM

FLAG	URP 36	anti - EpCam
MDYKDDDDKSPGSGEGGSGEGGSGEGGSGEGGSGEGGSGHTLECLGNICWVIN		
QGGEGSGEGGSGEGGSGEGGSGEGGSGEGGSGHTLECLGNICWVINQGGEGSGGEGGS		
GGE GSGEGGSGEGGSGEGGSGHTLECLGNICWVINQGGEGSGGEGSGGEGGSG		
GEGGSGEGGSGHTLECLGNICWVINQSSLEGTHHHHH	His tag	

Fig. 32. Buildup of binding modules by random sequence addition

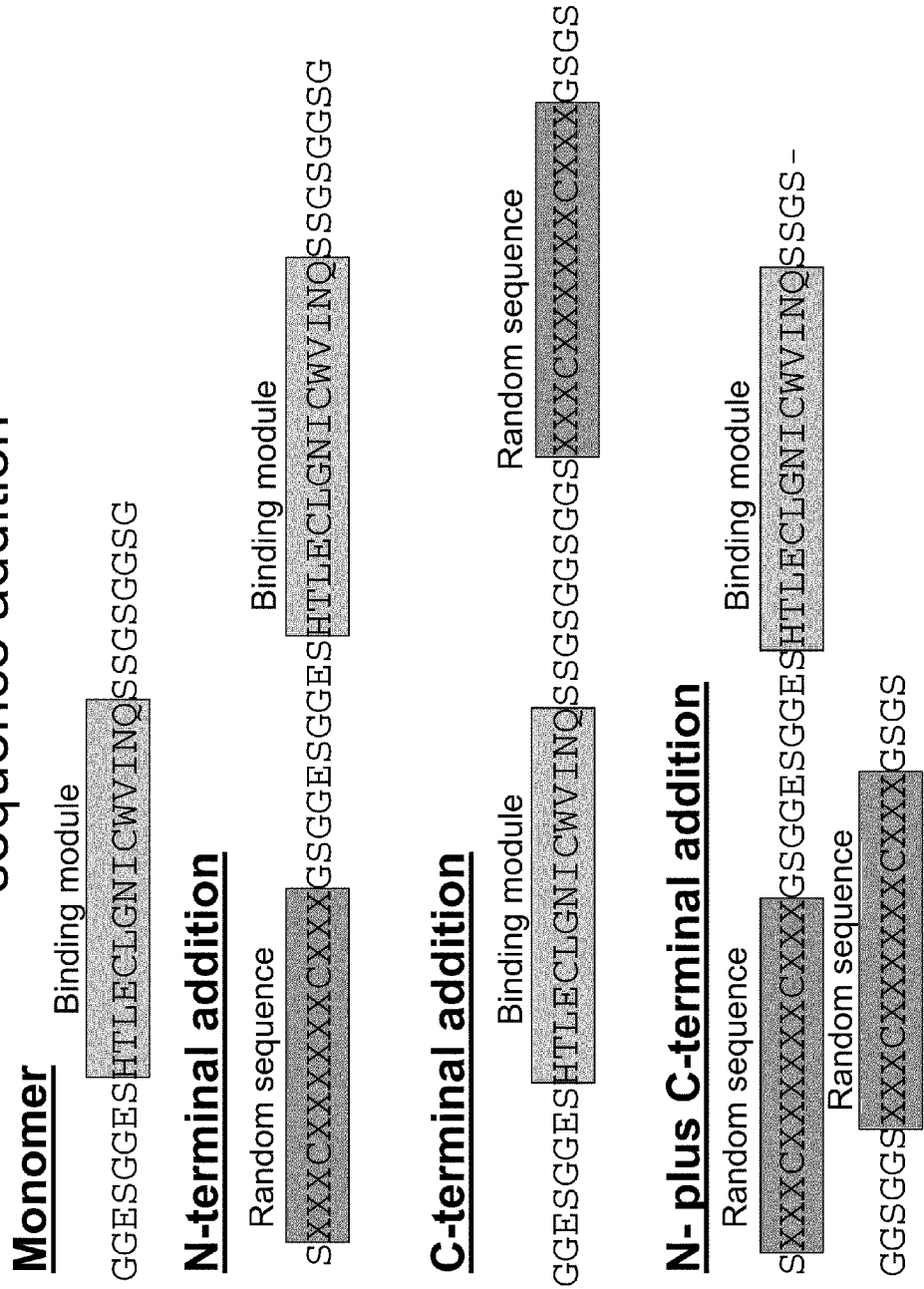


Fig. 34. Design of a 3FT library

SCHX₁X₂X₃X₄X₅X₆X₇X₈AVTCPPGENLCYRKMWX₉X₁₀X₁₁X₁₂X₁₃X₁₄X₁₅X₁₆X₁₇X₁₈X₁₉GCAATCPSVKPYEEVTCSTDKC
G

X₁ – MNW (HIKLPQRST)
 X₂ – VVK (AEGHKNPQRST)
 X₃ – 50% MVA (KPQRT) and 50% KMT (ADSY)
 X₄ – RVT (ADGNST)
 X₅ – MVW (HKNPQRST)
 X₆ – SCT (AP)
 X₇ – MNA (IKLPQRT)
 X₈ – RNM (ADEGIKNRSTV)
 X₉ – VKT (GILRSV)
 X₁₀ – SVT (ADGHPR)
 X₁₁ – RST (AGST)
 X₁₂ – WYA (ILST)
 X₁₃ – CST (PR)
 X₁₄ – GVG (AEG)
 X₁₅ – 50% RRG (EGKR) AND 50% WHT (FINSTY)
 X₁₆ – RDA (EGIKRV)
 X₁₇ – DYA (AILSTV)
 X₁₈ – RDM (DEGIKNRSV)
 X₁₉ – MKG (LMR)

Fig. 35. Alignment of Plexin sequences

CRHFQSCSQCLSAPPFVQCGWCHDKCVRSEECLSGTWTQQIC	MET_HUMAN/519-562
CEHFQSCSQCLSAPPFVQCGWCHNKCVRSEECPSGVWTQDVC	Q2IBC0_RHIFE/519-562
CEHFQSCSQCLSAPPFVQCGWCHDKCVRLETCPSGAWTQEIC	Q2QLD2_CARPS/119-162
CEHFQSCSQCLSAPPFVQCGWCHDKCVRSEECPSGSWTQETC	MET_OTOGA/520-563
CEHFQSCSQCLSAPPFVQCGWCQDKCVQLEECPSGTWTQEIC	Q2VHX7_PIG/519-562
CEHFQSCSQCLSAPPFVQCGWCHDRCVHLEECPTGAWTQEV	MET_CANFA/520-563
CGHFQSCSQCLSPFYFIQCGWCHNRCVHSNECPSGTWTQEIC	MET_RAT/520-563
CHHFQSCSQCLLAPAFMRGCGGQQCLRAPECNGGTWTQETC	Q90975_CHICK/519-562
CDHLTTCTSLVSSRVTECGWCEGRCTRANQCPPSVWTQEYC	Q9YGM7_FUGRU/528-571
CQHFLTCAVCLTAPKFVGGCGWCSGVCSESDCDHHW-RNDSC	Q9YGN0_FUGRU/512-554
CQHFLTCAVCLTAPKFVGGCGWCSGVCSEWENQCDDRW-RNESC	Q4SR43_TETNG/490-532
CAHFRTCSMCLMAPRFMNCGWCSGVCSRQHECTSQW-TSASC	Q4RXB0_TETNG/431-473
CAHFRTCSMCLMAPRFMNCGWCSGVCSRQHQCQDMQW-EKDSC	Q9YGM5_FUGRU/509-551
CRHF LTCGRCLRAWHFMGCGWCGNMCQQQKECPGSW-QQDHC	RON_HUMAN/526-568
CHHFLT CGSCLRAQRFMGCGWCGMCGRQKECPGSW-QQDHC	Q6DTW4_CANFA/118-160
CRHF LTCWRCLRAQRFMGCGWCGDRCDRQKECPGSW-QQDHC	RON_MOUSE/528-570
CRHFSTCDRCLRAERFMGCGWCGNGCTRHHECAGPW-VQDSC	Q08757_CHICK/521-563

Fig. 36. Design of Plexin libraries

N-terminal library

SCX₁HX₂X₃X₄CX₅X₆CLX₇X₈X₉X₁₀X₁₁X₁₂X₁₃CGWCHDKCVRSEECLSGTWTQQICG

X₁ - SRS (DEGHQR)
 X₂ - TTM (FL)
 X₃ - MNW (HIKLPQRST)
 X₄ - AST (ST)
 X₅ - DSG (AGRSTW)
 X₆ - MDG (KLMQR)
 X₇ - VKS (GILMRSV)
 X₈ - KCT (AS)
 X₉ - 75% SMA (AEPQ) and 25% TSG (SW)
 X₁₀ - SVK (ADEGHPQR)
 X₁₁ - KKT (FV)
 X₁₂ - RYS (AIMTV)
 X₁₃ - VRS (DEGHKNQRS)

C-terminal library

SCRHFQSCSQCLSAAPPFVQCGWCX₁X₂X₃CX₄X₅X₆X₇X₈CX₉X₁₀X₁₁(X₁₂)WX₁₃X₁₄X₁₅X₁₆CG

X₁ - VRT (DGHNRS)
 X₂ - RRT (DGNS)
 X₃ - RDG (EGKMRV)
 X₄ - RBT (AGISTV)
 X₅ - 75% CRM (HQR) and 25% TGG (W)
 X₆ - 50% KYH (SLA) and 50% SAM (DEHQ)
 X₇ - VAM (DEHKNQ)
 X₈ - SAM (DEHQ)
 X₉ - VMT (ADHNPT)
 X₁₀ - RVT (ADGNST)
 X₁₁ - VRS (DEGHKNQRS)
 Split with X₁₂ - DYT (AFISTV) and without
 X₁₃ - MVA (QRT)
 X₁₄ - MAM (HKNQ)
 X₁₅ - SAM (DEHQ)
 X₁₆ - NHT (ADFHILNPSTVY)

Fig. 37. Sequences of target-specific isolates from Plexin-based libraries

Library LMP031

SCXHXHXXCXXCLXXXXXXXXXCGWCHDKCVRSEECCLSGTWTQQICG

Library LMP032

SCRHFQSCSQCLSAAPPFVQCGWCXXXCXXXXXXCXXXXXXWXXXXXCG

Binders to DR4

SCHHFISGRC LRSWHVDCGWCHDKCVRSEEC LSGTWTQQICG D4.09

SCRHFQSCSQCLSA PPFVQCGWCGDMCARVQQCHDR-WTHHACG D4.01

SCRHFQSCSQCLSAAPPFVQCGWCHDKCGHQDECTAS-WRKEACG D4.03

Binders to ErbB2

SCRHFQSCSQCLSA PPFVQCGWCRNMCVQEFKQCDDSIWKNOHCG E2.39

SCRHFOCSQCLSA PPFVQCGWCRDRCSREDHCHPTKTWRNHPCG E2.56

SCRHF0SCSOCL5APPFVOCGWCNNVCSRHNDCDNN-WOHONCG E2.57

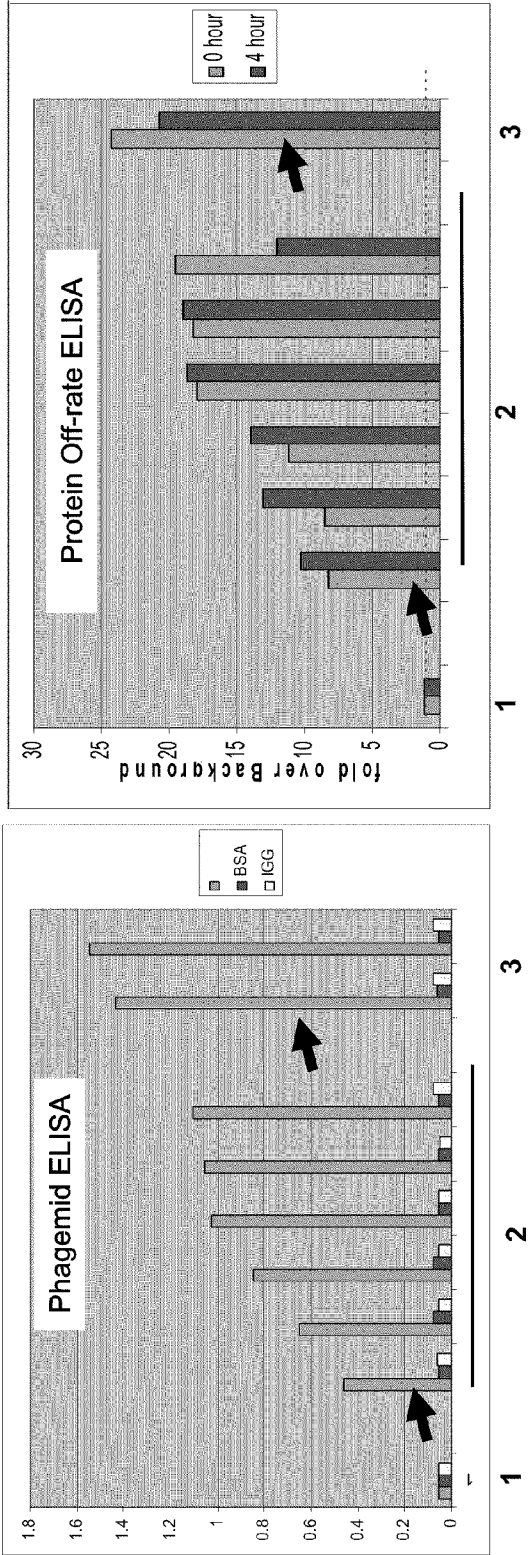
Binders to HGFR

SCRHF0SC0CLSAAPPFVOCGWCNSMCGRAHDC7DH - WOKOHCG CM.33

SCRHFOSCSOCLSA PPFVOCGWCGNMCVRSEECHTD-WRHDTCG CM.39

SCRHF0SC0CL5APPFVOCGWCNSMCGRAODCNDRTWK0HTCG CM.52

Fig. 38. Binding and expressing of 2SS VEGF- binders resulting from buildup



Affinity Maturation yields improved affinity without loss of specificity

Fig. 39. Expression and sequences of 2SS VEGF binders resulting from buildup libraries

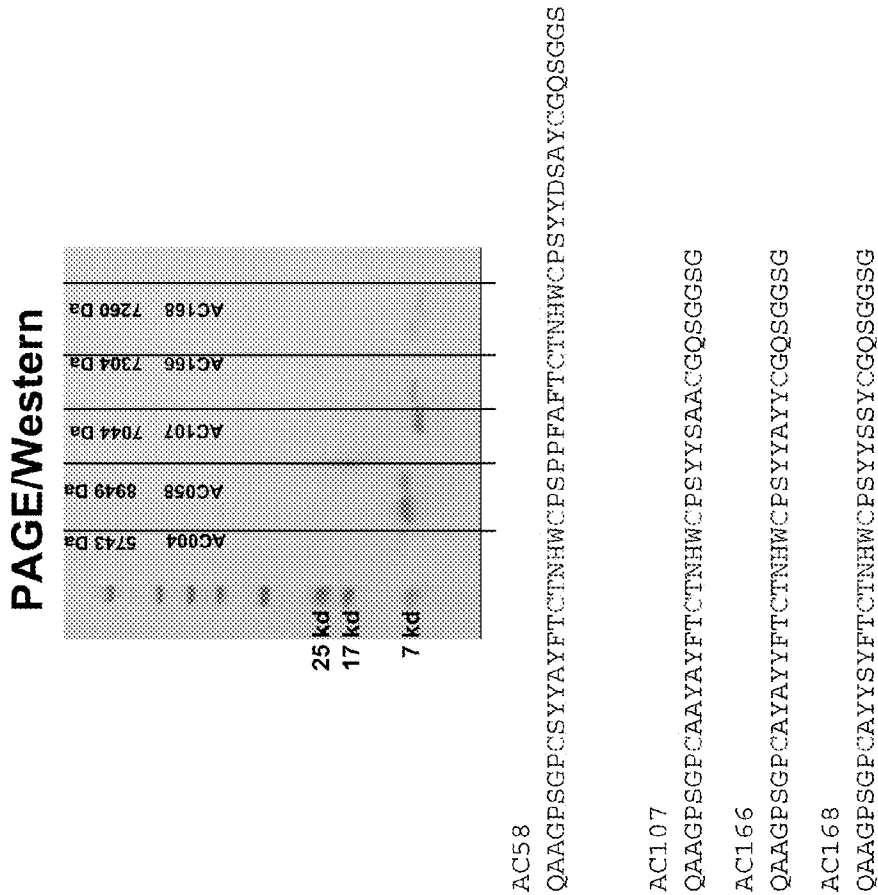


Fig. 40. Construction of rPEG_J72

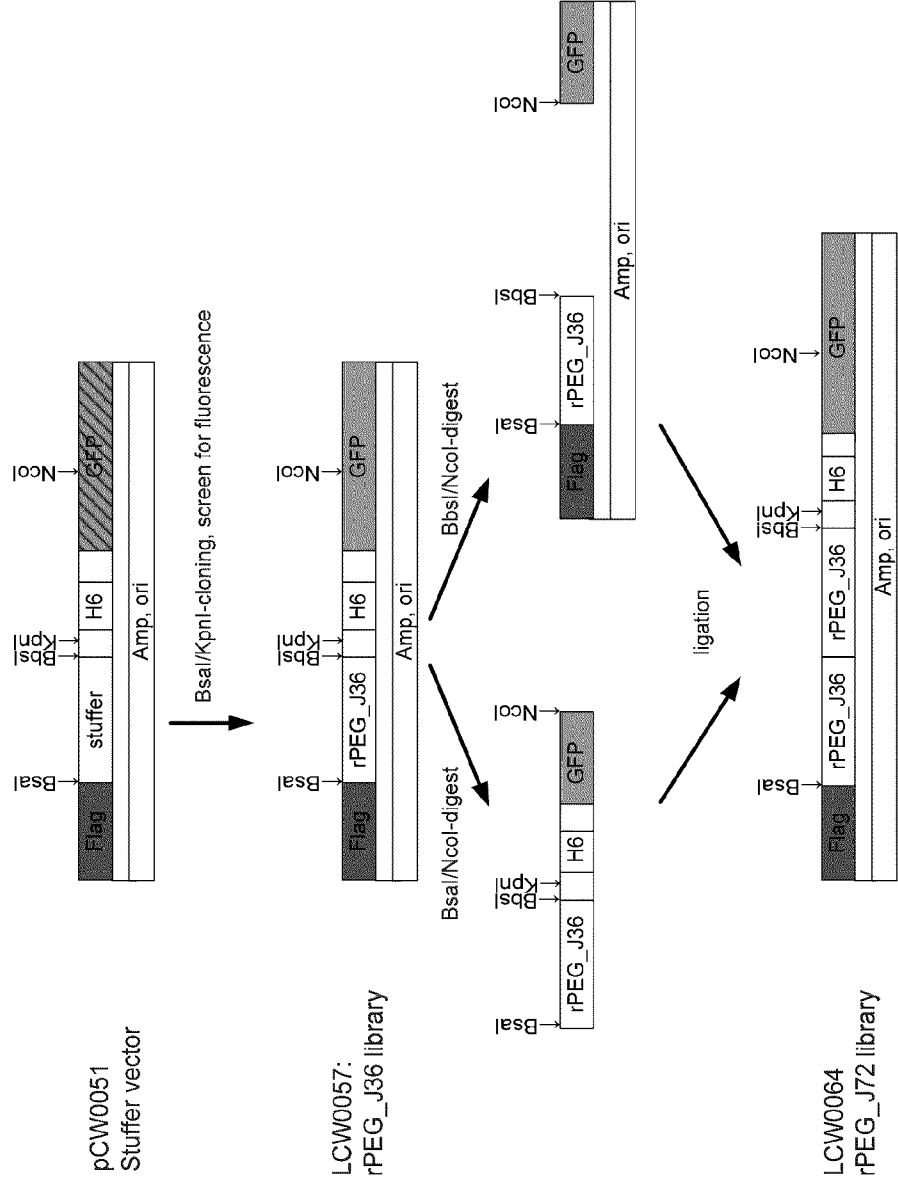


Fig. 41. Construction of an rPEG_J36 codon library

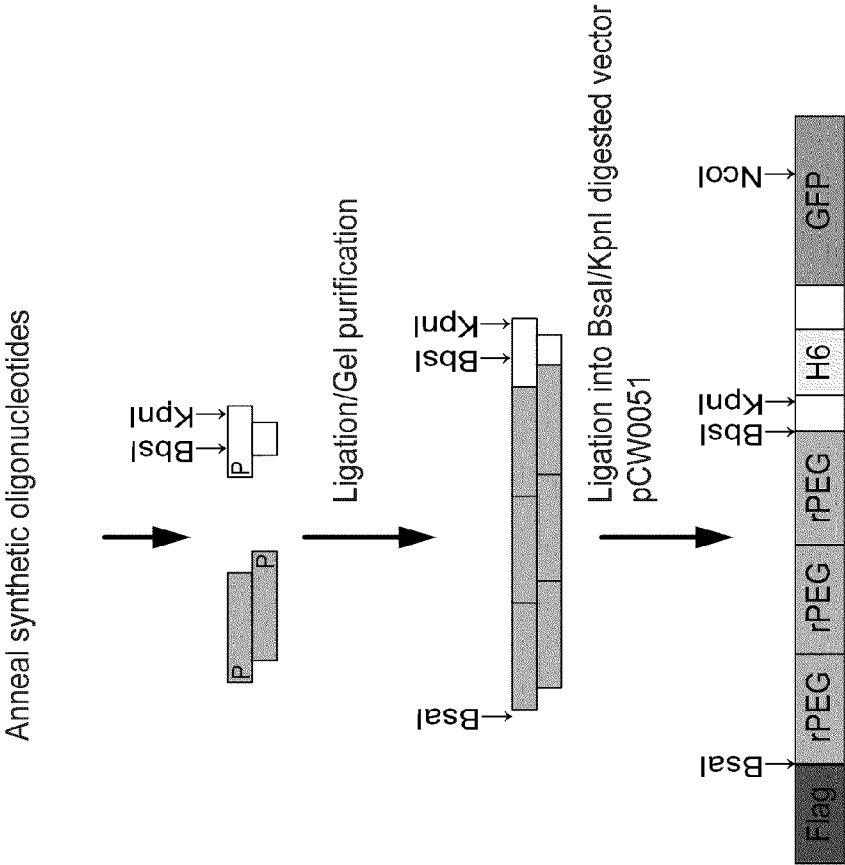


Fig. 43. Purification of Flag-rPEG_J288-H6-GFP

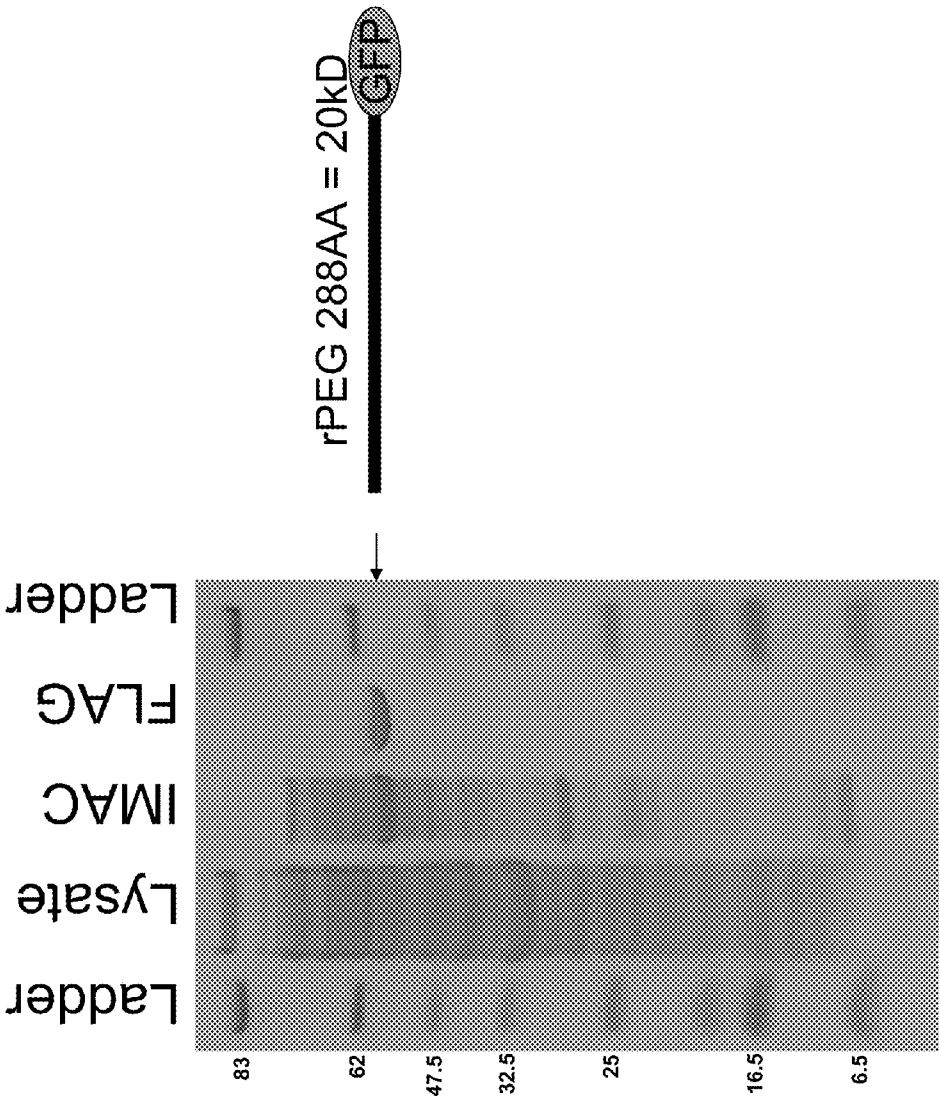


Fig. 44. Amino acid sequence of a fusion proteins between rPEG_{J288} and effector modules

Interferon-alpha 2a: 463aa, pI=4.27, MW=41698.0 (pC'W0084):

[illegible]

G-CSF: 472aa, pI=4.11, MW=41128.67 (pCW0085):

[illegible]

Human Growth Hormone: 489aa, pI=4.21, MW=44586.03 (pCW00083):

[illegible]

Fig. 45. Expresson of fusion proteins between
rPEG_J288 and human effector modules

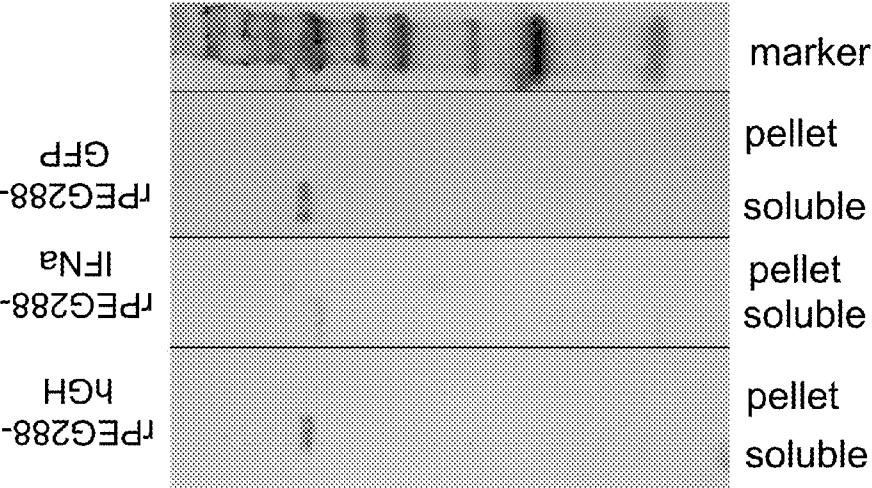


Fig. 46. Optimizing ion channel blockers

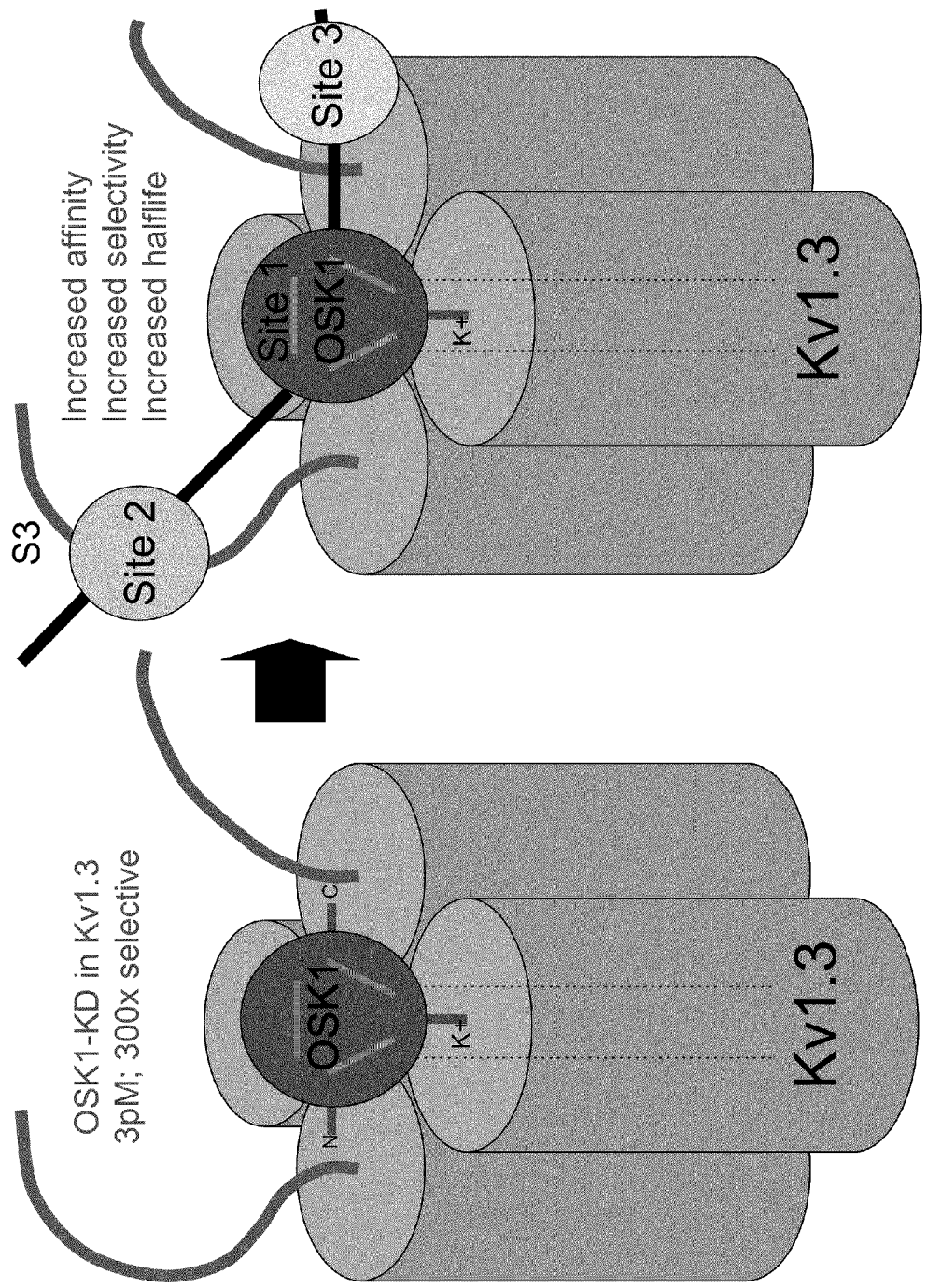
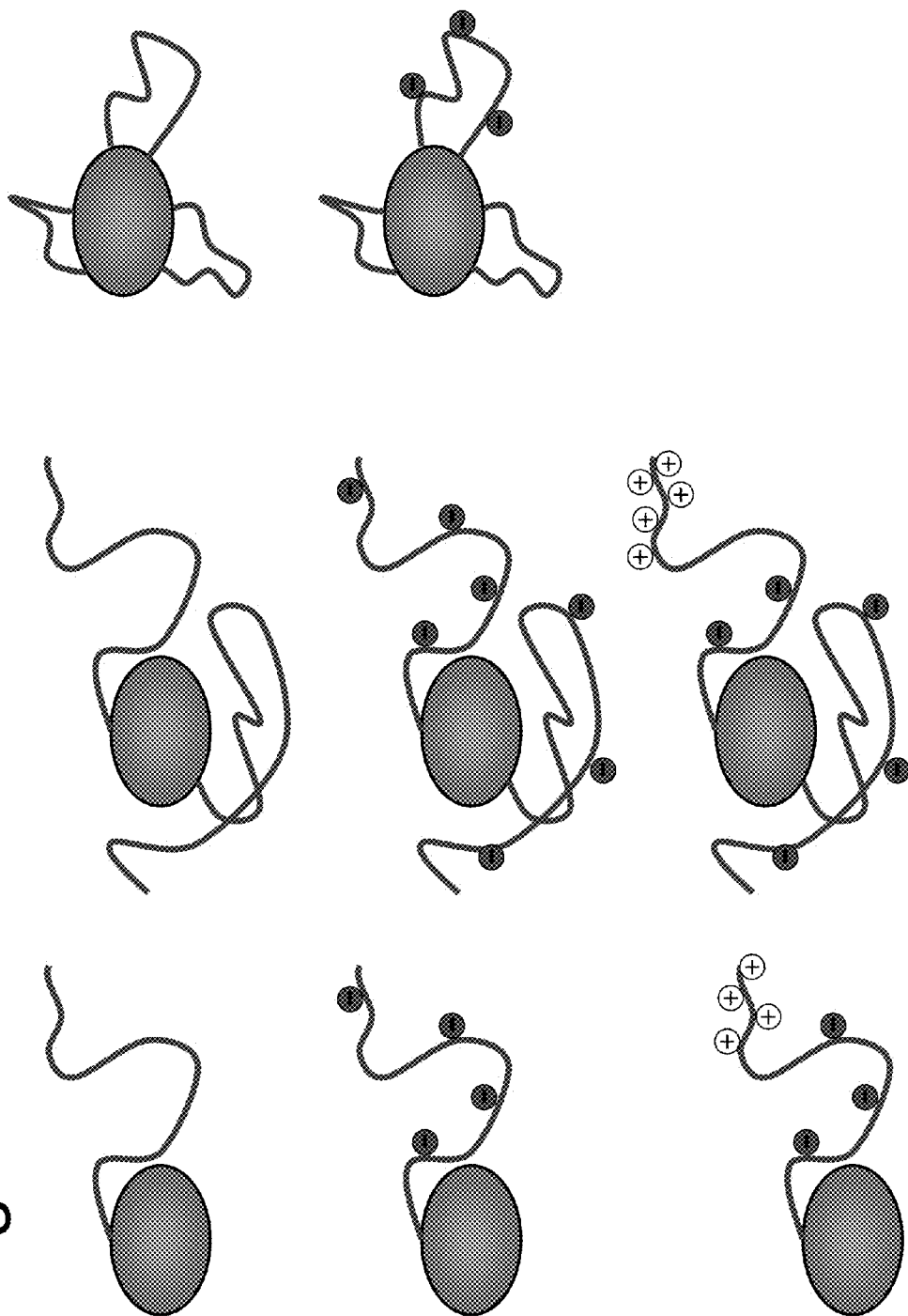


Figure 47. Product Formats



BIOLOGICALLY ACTIVE PROTEINS HAVING INCREASED IN VIVO AND/OR IN VITRO STABILITY

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 60/743,410 filed Mar. 6, 2006, which application is incorporated herein by reference. This application is a continuation-in-part application of Ser. Nos. 11/528,927 and 11/528,950, filed on Sep. 27, 2006, which in turn claim priority to provisional applications Ser. Nos. 60/721,270, 60/721,188, filed on Sep. 27, 2005 and 60/743,622 filed on Mar. 21, 2006, all of which are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] It has been well documented that properties of proteins, in particular plasma clearance and immunogenicity, can be improved by attaching hydrophilic polymers to these proteins (Kochendoerfer, G. (2003) *Expert Opin Biol Ther*, 3: 1253-61), (Greenwald, R. B., et al. (2003) *Adv Drug Deliv Rev*, 55: 217-50), (Harris, J. M., et al. (2003) *Nat Rev Drug Discov*, 2: 214-21). Examples of polymer-modified proteins that have been approved by the FDA for treatment of patients are Adagen, Oncaspar, PEG-Intron, Pegasys, Somavert, and Neulasta. Many more polymer-modified proteins are in clinical trials. These polymers exert their effect by increasing the hydrodynamic radius (also called Stokes' radius) of the modified protein relative to the unmodified protein, which reduces the rate of clearance by kidney filtration (Yang, K., et al. (2003) *Protein Eng*, 16: 761-70). In addition, polymer attachment can reduce interaction of the modified protein with other proteins, cells, or surfaces. In particular, polymer attachment can reduce interactions between the modified protein and antibodies and other components of the immune system thus reducing the formation of a host immune response to the modified protein. Of particular interest is protein modification by PEGylation, i.e. by attaching linear or branched polymers of polyethylene glycol. Reduced immunogenicity upon PEGylation was shown for example for phenylalanine ammonia lyase (Gamez, A., et al. (2005) *Mol Ther*, 11: 986-9), antibodies (Deckert, P. M., et al. (2000) *Int J Cancer*, 87: 382-90.), Staphylokinase (Collen, D., et al. (2000) *Circulation*, 102: 1766-72), and hemoglobin (Jin, C., et al. (2004) *Protein Pept Lett*, 11: 353-60). Typically, such polymers are conjugated with the protein of interest via a chemical modification step after the unmodified protein has been purified.

[0003] Various polymers can be attached to proteins. Of particular interest are hydrophilic polymers that have flexible conformations and are well hydrated in aqueous solutions. A frequently used polymer is polyethylene glycol (PEG). These polymers tend to have large hydrodynamic radii relative to their molecular weight (Kubetzko, S., et al. (2005) *Mol Pharmacol*, 68: 1439-54). The attached polymers tend to have limited interactions with the protein they have been attached to and thus the polymer-modified protein retains its relevant functions.

[0004] The chemical conjugation of polymers to proteins requires complex multi-step processes. Typically, the protein component needs to be produced and purified prior to the chemical conjugation step. The conjugation step can result in the formation of product mixtures that need to be separated leading to significant product loss. Alternatively, such mix-

tures can be used as the final pharmaceutical product. Some examples are currently marketed PEGylated Interferon-alpha products that are used as mixtures (Wang, B. L., et al. (1998) *J Submicrosc Cytol Pathol*, 30: 503-9; Dhalluin, C., et al. (2005) *Bioconjug Chem*, 16: 504-17). Such mixtures are difficult to manufacture and characterize and they contain isomers with reduced or no therapeutic activity.

[0005] Methods have been described that allow the site-specific addition of polymers like PEG. Examples are the selective PEGylation at a unique glycosylation site of the target protein or the selective PEGylation of a non-natural amino acid that has been engineered into the target proteins. In some cases it has been possible to selectively PEGylate the N-terminus of a protein while avoiding PEGylation of lysine side chains in the target protein by carefully controlling the reaction conditions. Yet another approach for the site-specific PEGylation of target proteins is the introduction of cysteine residues that allow selective conjugation. All these methods have significant limitations. The selective PEGylation of the N-terminus requires careful process control and side reactions are difficult to eliminate. The introduction of cysteines for PEGylation can interfere with protein production and/or purification. The specific introduction of non-natural amino acids requires specific host organisms for protein production. A further limitation of PEGylation is that PEG is typically manufactured as a mixture of polymers with similar but not uniform length. The same limitations are inherent in many other chemical polymers.

[0006] Chemical conjugation using multifunctional polymers which would allow the synthesis of products with multiple protein modules is even more complex than the polymer conjugation of a single protein domain.

[0007] Recently, it has been observed that some proteins of pathogenic organisms contain repetitive peptide sequences that seem to lead to a relatively long serum half-life of the proteins containing these sequences (Alvarez, P., et al. (2004) *J Biol Chem*, 279: 3375-81). It has also been demonstrated that oligomeric sequences that are based on such pathogen-derived repetitive sequences can be fused to other proteins resulting in increased serum half-life. However, these pathogen-derived oligomers have a number of deficiencies. The pathogen-derived sequences tend to be immunogenic. It has been described that the sequences can be modified to reduce their immunogenicity. However, no attempts have been reported to remove T cell epitopes from the sequences contributing to the formation of immune reactions. Furthermore, the pathogen-derived sequences have not been optimized for pharmacological applications which require sequences with good solubility and a very low affinity for other target proteins.

[0008] Thus there is a significant need for compositions and methods that would allow one to combine multiple polymer modules and multiple protein modules into defined multidomain products.

SUMMARY OF THE INVENTION

[0009] The present invention provides an unstructured recombinant polymer (URP) comprising at least 40 contiguous amino acids, wherein said URP is substantially incapable of non-specific binding to a serum protein, and wherein (a) the sum of glycine (G), aspartate (D), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P) residues contained in the URP, constitutes more than about 80% of the total amino acids of the URP; and/or (b) at least 50% of the

amino acids are devoid of secondary structure as determined by Chou-Fasman algorithm. In a related embodiment, the present invention provides an unstructured recombinant polymer (URP) comprising at least 40 contiguous amino acids, wherein said URP has an in vitro serum degradation half-life greater than about 24 hours, and wherein (a) the sum of glycine (G), aspartate (D), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P) residues contained in the URP, constitutes more than about 80% of the total amino acids of the URP; and/or (b) at least 50% of the amino acids are devoid of secondary structure as determined by Chou-Fasman algorithm. The subject URP can comprises a non-natural amino acid sequence. Where desired, the URP is selected for incorporation into a heterologous protein, and wherein upon incorporation the URP into a heterologous protein, said heterologous protein exhibits a longer serum secretion half-life and/or higher solubility as compared to the corresponding protein that is deficient in said URP. The half-life can be extended by two folds, three folds, five folds, ten folds or more. In some aspects, incorporation of the URP into a heterologous protein results in at least a 2-fold, 3-fold, 4-fold, 5-fold or more increase in apparent molecular weight of the protein as approximated by size exclusion chromatography. In some aspects, the URPs has a Tepitope score less than -3.5 (e.g., -4 or less, -5 or less). In some aspects, the URPs can contain predominantly hydrophilic residues. Where desired, at least 50% of the amino acids of the URP are devoid of secondary structure as determined by Chou-Fasman algorithm. The glycine residues contained in the URP may constitute at least about 50% of the total amino acids of the URP. In some aspect, any one type of the amino acids alone selected from the group consisting of glycine (G), aspartate (D), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P) contained in the URP constitutes more than about 20%, 30%, 40%, 50%, 60% or more of the total amino acids of the URP. In some aspects, the URP comprises more than about 100, 150, 200 or more contiguous amino acids.

[0010] The present invention also provides a protein comprising one or more of the subject URPs, wherein the subject URPs are heterologous with respect to the protein. The total length of URPs in aggregation can exceed about 40, 50, 60, 100, 150, 200, or more amino acids. The protein can comprise one or more functional modules selected from the group consisting of effector module, binding module, N-terminal module, C-terminal module, and any combinations thereof. Where desired, the subject protein comprises a plurality of binding modules, wherein the individual binding modules exhibit binding specificities to the same or different targets. The binding module may comprise a disulfide-containing scaffold formed by intra-scaffold pairing of cysteines. The binding module may bind to a target molecule target is selected from the group consisting of cell surface protein, secreted protein, cytosolic protein, and nuclear protein. The target can be an ion channel and/or GPCR. Where desired, the effector module can be a toxin. The subject URP-containing protein typically an extended serum secretion half-life by at least 2, 3, 4, 5, 10 or more folds as compared to a corresponding protein that is deficient in said URP.

[0011] In a separate embodiment, the present invention provides a non-naturally occurring protein comprising at least 3 repeating units of amino acid sequences, each of the repeating unit comprising at least 6 amino acids, wherein the majority of segments comprising about 6 to about 15 contiguous

amino acids of the at least 3 repeating units are present in one or more native human proteins. In one aspect, the majority of the segments, or each segment comprising about 9 to about 15 contiguous amino acids within the repeating units are present in one or more native human proteins. The segments can comprise about 9 to about 15 amino acids. The three repeating units may share substantial sequence homology, e.g., share sequence identify of greater than about 50%, 60%, 70%, 80%, 90% or 100% when aligned. Such non-natural protein may also comprise one or more modules selected from the group consisting of binding modules, effector modules, multimerization modules, C-terminal modules, and N-terminal modules. Where desired, the non-natural protein may comprise individual repeating unit having the subject unstructured recombinant polymer (URP).

[0012] The present invention also provides recombinant polynucleotides comprising coding sequences that encode the subject URPs, URP-containing proteins, microproteins and toxins. Also provided in the present invention are vectors containing the subject polynucleotides, host cells harboring the vectors, genetic packages displaying the subject URPs, URP-containing proteins, toxins and any other proteinaceous entities disclosed herein. Further provided are selectable library of expression vectors of the present invention.

[0013] The present invention also provides method of producing a protein comprising an unstructured recombinant polymer (URP). The method involves (i) providing a host cell comprising a recombinant polynucleotide encoding the protein, said protein comprising one or more URP, said URP comprising at least 40 contiguous amino acids, wherein said URP is substantially incapable of non-specific binding to a serum protein, and wherein (a) the sum of glycine (G), aspartate (D), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P) residues contained in the URP, constitutes more than about 80% of the total amino acids of the URP; and/or (b) at least 50% of the amino acids are devoid of secondary structure as determined by Chou-Fasman algorithm; and (ii) culturing said host cell in a suitable culture medium under conditions to effect expression of said protein from said polynucleotide. Suitable host cells are eukaryotic (e.g., CHO cells) and prokaryotic cells.

[0014] The present invention also provides a method of increasing-serum secretion half-life of a protein, comprising: fusing said protein with one or more unstructured recombinant polymers (URPs), wherein the URP comprises at least about 40 contiguous amino acids, and wherein (a) the sum of glycine (G), aspartate (D), alanine (A), serine (S), threonine (T), glutamate (E) and proline (P) residues contained in the URP, constitutes more than about 80% of the total amino acids of the URP; and/or (b) at least 50% of the amino acids are devoid of secondary structure as determined by Chou-Fasman algorithm; and wherein said URP is substantially incapable of non-specific binding to a serum protein.

[0015] Also provided in the present invention is a method of detecting the presence or absence of a specific interaction between a target and an exogenous protein that is displayed on a genetic package, wherein said protein comprises one or more unstructured recombinant polymer (URP), the method comprising: (a) providing a genetic package displaying a protein that comprises one or more unstructured recombinant polymers (URPs); (b) contacting the genetic package with the target under conditions suitable to produce a stable protein-target complex; and (c) detecting the formation of the stable protein-target complex on the genetic package, thereby

detecting the presence of a specific interaction. The method may further comprises obtaining a nucleotide sequence from the genetic package that encodes the exogenous protein. In some aspects, the presence or absence of a specific interaction is between the URP and a target comprising a serum protein. In some aspects, the presence or absence of a specific interaction is between the URP and a target comprising a serum protease.

[0016] Further included in the present invention is a genetic package displaying a microprotein, wherein said microprotein retains binding capability to its native target. In some aspects, the microprotein exhibits binding capability towards at least one family of ion channel selected from the group consisting of a sodium, a potassium, a calcium, an acetylcholine, and a chlorine channel. Where desired, the microprotein is an ion-channel-binding microprotein, and is modified such that (a) the microprotein binds to a different family of channel as compared to the corresponding unmodified microprotein; (b) the microprotein binds to a different subfamily of the same channel family as compared to the corresponding unmodified microprotein; (c) the microprotein binds to a different species of the same subfamily of channel as compared to the corresponding unmodified microprotein; (d) the microprotein binds to a different site on the same channel as compared to the corresponding unmodified microprotein; and/or (e) the microprotein binds to the same site of the same channel but yield a different biological effect as compared to the corresponding unmodified microprotein. In some aspect, the microprotein is a toxin. The present invention also provides a library of genetic packages displaying the subject microproteins and/or toxins. Where desired, the genetic package displays a proteinaceous toxin that retains in part or in whole its toxicity spectrum. The toxin can be derived from a single toxin protein, or derived from a family of toxins. The present invention also provides a library of genetic packages wherein the library displays a family of toxins, wherein the family retains in part or in whole its native toxicity spectrum.

[0017] The present invention further provides a protein comprising a plurality of ion-channel binding domains, wherein individual domains are microprotein domains that have been modified such that (a) the microprotein domains bind to a different family of channel as compared to the corresponding unmodified microprotein domains; (b) the microprotein domains bind to a different subfamily of the same channel family as compared to the corresponding unmodified microprotein domains; (c) the microprotein domains bind to a different species of the same subfamily as compared to the corresponding unmodified microprotein domains; (d) the microprotein domains bind to a different site on the same channel as compared to the corresponding unmodified microprotein domains; (e) the microprotein domains bind to the same site of the same channel but yield a different biological effect as compared to the corresponding unmodified microprotein domains; and/or (f) the microprotein domains bind to the same site of the same channel and yield the same biological effect as compared to the corresponding unmodified microprotein domains.

[0018] Also embodied in the invention is a method of obtaining a microprotein with desired property, comprising: (a) providing a subject library; and (b) screening the selectable library to obtain at least one phage displaying a micro-

protein with the desired property. Polynucleotides, vectors, genetic packages, host cells for use in any one of the disclosed methods are also provided.

INCORPORATION BY REFERENCE

[0019] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0021] FIG. 1 shows the modular components of an MURP. Binding modules, effector modules, and multimerization modules are depicted as circles. URP modules, N-terminal, and C-terminal modules are shown as rectangles.

[0022] FIG. 2 shows examples of modular architectures of MURPs. Binding modules (BM) in one MURP can have identical or differing target specificities.

[0023] FIG. 3 shows that a repeat protein that is based on a human sequence can contain novel amino acid sequences, which can contain T cell epitopes. These novel sequences are formed at the junction between neighboring repeat units.

[0024] FIG. 4 illustrates the design of a URP sequence that is a repeat protein based on three human donor sequences D1, D2, and D3. The repeating unit of this URP was chosen such that even 9-mer sequences that span the junction between neighboring units can be found in at least one of the human donor sequences.

[0025] FIG. 5 Example of a URP sequences that is a repeat protein based on the sequences of three human proteins. The lower portion of the figure illustrates that all 9-mer subsequences in the URP occur in at least one of the human donor proteins.

[0026] FIG. 6 Example based URP sequence based on the human POU domain residues 146-182.

[0027] FIG. 7 shows the advantage of separating modules with information rich sequences by inserting URP modules between such sequences. The left side of the figure shows that the direct fusion of modules A and B leads to novel sequences in the junction region. These junction sequences can be epitopes. The right half of the figure shows that the insertion of a URP module between module A and B prevents the formation of such junction sequences that contain partial sequences from modules A and B. Instead, the termini of modules A and B yield junction sequences that contain URP sequences and thus are predicted to have low immunogenicity.

[0028] FIG. 8 shows drug delivery constructs that are based on URPs. The drug molecules depicted as hexagons are chemically conjugated to the MURP.

[0029] FIG. 9 shows and MURP containing a protease-sensitive site. The URP module is designed such that it blocks the effector module from its function. Protease cleavage removes a portion of the URP module and results in increased activity of the effector function.

[0030] FIG. 10 shows how an URP module can act as a linker between a binding module and an effector module. The binding module can bind to a target and as a consequence it increases the local concentration of the effector module in the proximity of the target.

[0031] FIG. 11 Shows a process to construct genes encoding URP sequences from libraries of short URP modules. The URP module library can be inserted into a stuffer vector that contains green fluorescent protein (GFP) as a reporter to facilitate the identification of URP sequences with high expression. The figure illustrates that genes encoding long URP sequences can be build by iterative dimerization.

[0032] FIG. 12 shows MURPs that contain multiple binding modules for death receptors. Death receptors are triggered by trimerization and thus MURPs containing at least three binding elements for one death receptor particularly potent in inducing cell death. The lower portion of the figure illustrates that one can increase the specificity of the MURP for diseased tissue by adding one or more binding modules with specificity for tumor tissue.

[0033] FIG. 13 shows a MURP that comprises four binding modules (rectangles) with specificity for a tumor antigen with an effector module like interleukin 2.

[0034] FIG. 14 shows the flow chart for the construction of URP modules with 288 residues. The URP modules were constructed as fusion proteins with GFP. Libraries of URP modules with 36 amino acids were constructed first followed by iterative dimerization to yield URP modules with 288 amino acids (rPEG_H288 and rPEG_J288).

[0035] FIG. 15 Amino acid and nucleotide sequence of a URP module with 288 amino acids (rPEG_J288).

[0036] FIG. 16 Amino acid and nucleotide sequence of a URP module with 288 amino acids (rPEG_H288).

[0037] FIG. 17 Amino acid sequence of a serine-rich sequence region of the human protein dentin sialophosphoprotein.

[0038] FIG. 18 shows a depot derivative of a MURP. The protein contains two cysteine residues that can form a weak SS bridge. The protein can be manufactured with the SS bridge intact. It can be formulated and injected into patients in reduced form. After injection it will be oxidized in proximity to the injection site and as a result in can form a high molecular weight polymer with very limited diffusivity. The active MURP can slowly leach from the injection site by limited proteolysis or limited reduction of the cross linking SS bond.

[0039] FIG. 19 shows a depot form of a MURP. The MURP has very limited diffusivity at the injection site and can be liberated from the injection site by limited proteolysis.

[0040] FIG. 20 shows a depot form of a MURP that contains a histidine-rich sequence. The MURP can be formulated and injected in combination with insoluble beads that contain immobilized nickel. The MURP binds to the nickel beads at the injection site and is released slowly into the circulation.

[0041] FIG. 21 shows MURPs that contain multimerization modules. The upper part of the figure shows an MURP that contains one dimerization sequence. As a result it forms a dimer which effectively doubles its molecular weight. The center of the figure shows three MURP designs that comprise two multimerization sequences. Such MURPs can form multimers with very high effective molecular weight. The lower part of the figure illustrated an MURP that contains multiple RGD sequences that are known to bind to cell surface receptors and thus confer half-life.

[0042] FIG. 22 Shows a variety of MURPs that are designed to block or modulate ion channel function. Circles indicate binding modules with specificity for ion channels. These binding modules can be derived or identical to natural toxins with affinity for ion channel receptors. The figure illustrates that other binding domains can be added on either side of the ion channel-specific binding modules thus conferring the MURPs increased efficacy or specificity for a particular cell type.

[0043] FIG. 23 shows several MURP designs for increased half-life. Increased effective molecular weight can be achieved by increasing chain length (A), chemical multimerization (B), adding multiple copies of binding modules into a molecule separated by non-binding sites (C), construction of chemical multimers similar to C (D, E), including multimerization sequences (F).

[0044] FIG. 24 shows MURPs that can be formed by chemical conjugation of binding modules to a recombinant URP sequence. The URP sequence is designed to contain multiple lysine residues (K) as conjugation sites.

[0045] FIG. 25 shows the design of a library of 2SS binding modules. The sequences contain a constant 1SS sequence in the center which is flanked by random sequences that contain cysteine residues in varying distance from the 1SS core.

[0046] FIG. 26 shows the design of a library of 2SS binding modules. The sequences contain a constant 1SS sequence in the center which is flanked by random sequences that contain cysteine residues in varying distance from the 1SS core.

[0047] FIG. 27 shows the design of a library of dimers of 1SS binding modules. Initially, a collection of 1SS binding modules is amplified by two PCR reactions. The resulting PCR products are combined and dimers are generated in a subsequent PCR step.

[0048] FIG. 28 show the Western analysis of a fusion protein containing the 288 amino acid URP sequence rPEG_J288 after incubation of up to 3 days in 50% mouse serum.

[0049] FIG. 29 shows results of a binding assay testing for pre-existing antibodies against a URP sequence of 288 amino acids.

[0050] FIG. 30 shows the binding of MURPs containing one (Monomer), two (Dimer), four (Tetramer), or zero (rPEG36) binding modules with specificity for VEGF which was coated to microtiter plates.

[0051] FIG. 31 shows the amino acid sequence of an MURP with specificity for EpCAM. The sequence contains four binding modules with affinity for EpCAM (underlined). The sequence contains an N-terminal Flag sequence which contains the only two lysine residues of the entire sequence.

[0052] FIG. 32 shows the design of 1SS addition libraries. Random 1SS modules can be added to the N- or C-terminus of a pre-selected binding module or simultaneously to both sides.

[0053] FIG. 33 shows the alignment of three finger toxin-related sequences. The figure also shows a 3D structure that was solved by NMR.

[0054] FIG. 34 shows the design of a three-finger toxin-based library. Residues designated X were randomized. The codon choice for each random position is indicated.

[0055] FIG. 35 shows the alignment of plexin-related sequences.

[0056] FIG. 36 shows the design of a plexin-based library. Residues designated X were randomized. The codon choice for each random position is indicated.

[0057] FIG. 37 Sequences of plexin-related binding modules with specificity for DR4, ErbB2, and HGFR.

[0058] FIG. 38 shows a binding assay for microprotein-based binding domains with specificity for VEGF.

[0059] FIG. 39 shows sequences of 2SS and 3SS binding modules that were isolated from buildup libraries with specificity for VEGF. The upper part of the protein shows PAGE gel analysis of the proteins purified by heat-lysis.

[0060] FIG. 40 shows cloning steps to construct the URP sequence rPEG_J72.

[0061] FIG. 41 shows the construction of a library of URP modules with 36 amino acids called rPEG_J36. The region encoding rPEG_J36 was assembled by ligating three shorter segments encoding rPEG_J12 and a stopper module.

[0062] FIG. 42 shows the nucleotide sequence and translation of the stuffer vector pCW0051. The stuffer region is flanked by BsaI and BbsI sites and contains multiple stop codons.

[0063] FIG. 43 shows a PAGE gel of the purification of the URP rPEG_J288 fused to GFP. Lane 2 shows the cell lysate; lane 3: product purified by IMAC; lane 4: product purified by anti-Flag.

[0064] FIG. 44 Amino acid sequence of fusion proteins between rPEG_J288 and human effector domains interferon alpha, G-CSF, and human growth hormone.

[0065] FIG. 45 shows the Western analysis of expression of fusion proteins between rPEG_J288 and human growth hormone (lanes 1 and 2), interferon alpha (lanes 3 and 4), and GFP (lanes 5 and 6). Both soluble and insoluble material was analyzed for each protein.

[0066] FIG. 46 shows the design of MURPs based on the toxin OSK1. The figure shows that URP sequences and/or binding modules can be added to either side of OSK1

[0067] FIG. 47 depicts exemplary product formats comprising the subject URPs.

DETAILED DESCRIPTION OF THE INVENTION

[0068] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

General Techniques:

[0069] The practice of the present invention employs, unless otherwise indicated, conventional techniques of immunology, biochemistry, chemistry, molecular biology, microbiology, cell biology, genomics and recombinant DNA, which are within the skill of the art. See Sambrook, Fritsch and Maniatis, *MOLECULAR CLONING: A LABORATORY MANUAL*, 2nd edition (1989); *CURRENT PROTOCOLS IN MOLECULAR BIOLOGY* (F. M. Ausubel, et al. eds., (1987)); the series *METHODS IN ENZYMOLOGY* (Academic Press, Inc.); *PCR 2: A PRACTICAL APPROACH* (M. J. MacPherson, B. D. Hames and G. R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) *ANTIBODIES*, A

LABORATORY MANUAL, and *ANIMAL CELL CULTURE* (R. I. Freshney, ed. (1987)).

DEFINITIONS

[0070] As used in the specification and claims, the singular form “a”, “an” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a cell” includes a plurality of cells, including mixtures thereof.

[0071] The terms “polypeptide”, “peptide”, “amino acid sequence” and “protein” are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified, for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. As used herein the term “amino acid” refers to either natural and/or unnatural or synthetic amino acids, including but not limited to glycine and both the D or L optical isomers, and amino acid analogs and peptidomimetics. Standard single or three letter codes are used to designate amino acids.

[0072] A “repetitive sequence” refers to an amino acid sequence that can be described as an oligomer of repeating peptide sequences, forming direct repeats, or inverted repeats or alternating repeats of multiple sequence motifs. These repeating oligomer sequences can be identical or homologous to each other, but there can also be multiple repeated motifs. Repetitive sequences are characterized by a very low information content. A repetitive sequence is not a required feature of a URP and in some cases a non-repetitive sequence will in fact be preferred.

[0073] Amino acids can be characterized based on their hydrophobicity. A number of scales have been developed. An example is a scale developed by Levitt, M et al. (see Levitt, M (1976) *J Mol Biol* 104, 59, #3233, which is listed in Hopp, T P, et al. (1981) *Proc Natl Acad Sci USA* 78, 3824, #3232). Examples of “hydrophilic amino acids” are arginine, lysine, threonine, alanine, asparagine, and glutamine. Of particular interest are the hydrophilic amino acids aspartate, glutamate, and serine, and glycine. Examples of “hydrophobic amino acids” are tryptophan, tyrosine, phenylalanine, methionine, leucine, isoleucine, and valine.

[0074] The term “denatured conformation” describes the state of a peptide in solution that is characterized by a large conformational freedom of the peptide backbone. Most peptides and proteins adopt a denatured conformation in the presence of high concentrations of denaturants or at elevated temperatures. Peptides in denatured conformation have characteristic CD spectra and they are generally characterized by a lack of long range interactions as determined by e.g., NMR. Denatured conformation and unfolded conformation will be used synonymously.

[0075] The terms “unstructured protein (UNP) sequences” and “unstructured recombinant polymer” (URP) are used herein interchangeably. The terms refer to amino acid sequences that share commonality with denatured peptide sequences, e.g., exhibiting a typical behavior like denatured peptide sequences, under physiological conditions, as detailed herein. URP sequences lack a defined tertiary structure and they have limited or no secondary structure as detected by, e.g., Chou-Fasman algorithm.

[0076] As used herein, the term “cell surface proteins” refers to the plasma membrane components of a cell. It

encompasses integral and peripheral membrane proteins, glycoproteins, polysaccharides and lipids that constitute the plasma membrane. An integral membrane protein is a trans-membrane protein that extends across the lipid bilayer of the plasma membrane of a cell. A typical integral membrane protein consists of at least one membrane spanning segment that generally comprises hydrophobic amino acid residues. Peripheral membrane proteins do not extend into the hydrophobic interior of the lipid bilayer and they are bound to the membrane surface via covalent or noncovalent interaction directly or indirectly with other membrane components.

[0077] The terms “membrane”, “cytosolic”, “nuclear” and “secreted” as applied to cellular proteins specify the extracellular and/or subcellular location in which the cellular protein is mostly, predominantly, or preferentially localized.

[0078] “Cell surface receptors” represent a subset of membrane proteins, capable of binding to their respective ligands. Cell surface receptors are molecules anchored on or inserted into the cell plasma membrane. They constitute a large family of proteins, glycoproteins, polysaccharides and lipids, which serve not only as structural constituents of the plasma membrane, but also as regulatory elements governing a variety of biological functions.

[0079] The term “module” refers to a portion of a protein that is physically or functionally distinguished from other portions of the protein or peptide. A module can comprise one or more domains. In general, a module or domain can be a single, stable three-dimensional structure, regardless of size. The tertiary structure of a typical domain is stable in solution and remains the same whether such a member is isolated or covalently fused to other domains. A domain generally has a particular tertiary structure formed by the spatial relationships of secondary structure elements, such as beta-sheets, alpha helices, and unstructured loops. In domains of the microprotein family, disulfide bridges are generally the primary elements that determine tertiary structure. In some instances, domains are modules that can confer a specific functional activity, such as avidity (multiple binding sites to the same target), multi-specificity (binding sites for different targets), half-life (using a domain, cyclic peptide or linear peptide) which binds to a serum protein like human serum albumin (HSA) or to IgG (hIgG1, 2, 3 or 4) or to red blood cells. Functionally-defined domains have a distinct biological function(s). The ligand-binding domain of a receptor, for example, is that domain that binds ligand. An antigen-binding domain refers to the part of an antigen-binding unit or an antibody that binds to the antigen. Functionally-defined domains need not be encoded by contiguous amino acid sequences. Functionally-defined domains may contain one or more physically-defined domain. Receptors, for example, are generally divided into the extracellular ligand-binding domain, a transmembrane domain, and an intracellular effector domain. A “membrane anchorage domain” refers to the portion of a protein that mediates membrane association. Generally, the membrane anchorage domain is composed of hydrophobic amino acid residues. Alternatively, the membrane anchorage domain may contain modified amino acids, e.g. amino acids that are attached to a fatty acid chain, which in turn anchors the protein to a membrane.

[0080] “Non-naturally occurring” as applied to a protein means that the protein contains at least one amino acid that is different from the corresponding wildtype or native protein. Non-natural sequences can be determined by performing BLAST search using, e.g., the lowest smallest sum probabil-

ity where the comparison window is the length of the sequence of interest (the queried) and when compared to the non-redundant (“nr”) database of Genbank using BLAST 2.0. The BLAST 2.0 algorithm, which is described in Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information.

[0081] A “host cell” includes an individual cell or cell culture which can be or has been a recipient for the subject vectors. Host cells include progeny of a single host cell. The progeny may not necessarily be completely identical (in morphology or in genomic or total DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a vector of this invention.

[0082] As used herein, the term “isolated” means separated from constituents, cellular and otherwise, in which the polynucleotide, peptide, polypeptide, protein, antibody, or fragments thereof, are normally associated with in nature. As is apparent to those of skill in the art, a non-naturally occurring the polynucleotide, peptide, polypeptide, protein, antibody, or fragments thereof, does not require “isolation” to distinguish it from its naturally occurring counterpart. In addition, a “concentrated”, “separated” or “diluted” polynucleotide, peptide, polypeptide, protein, antibody, or fragments thereof, is distinguishable from its naturally occurring counterpart in that the concentration or number of molecules per volume is greater than “concentrated” or less than “separated” than that of its naturally occurring counterpart.

[0083] “Linked” and “fused” or “fusion” are used interchangeably herein. These terms refer to the joining together of two more chemical elements or components, by whatever means including chemical conjugation or recombinant means. An “in-frame fusion” refers to the joining of two or more open reading frames (ORFs) to form a continuous longer ORF, in a manner that maintains the correct reading frame of the original ORFs. Thus, the resulting recombinant fusion protein is a single protein containing two or more segments that correspond to polypeptides encoded by the original ORFs (which segments are not normally so joined in nature.)

[0084] In the context of polypeptides, a “linear sequence” or a “sequence” is an order of amino acids in a polypeptide in an amino to carboxyl terminus direction in which residues that neighbor each other in the sequence are contiguous in the primary structure of the polypeptide. A “partial sequence” is a linear sequence of part of a polypeptide which is known to comprise additional residues in one or both directions.

[0085] “Heterologous” means derived from a genotypically distinct entity from the rest of the entity to which it is being compared. For example, a glycine rich sequence removed from its native coding sequence and operatively linked to a coding sequence other than the native sequence is a heterologous glycine rich sequence. The term “heterologous” as applied to a polynucleotide, a polypeptide, means that the polynucleotide or polypeptide is derived from a genotypically distinct entity from that of the rest of the entity to which it is being compared.

[0086] The terms “polynucleotides”, “nucleic acids”, “nucleotides” and “oligonucleotides” are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three-dimensional structure, and may perform any function, known or

unknown. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component.

[0087] “Recombinant” as applied to a polynucleotide means that the polynucleotide is the product of various combinations of cloning, restriction and/or ligation steps, and other procedures that result in a construct that is distinct from a polynucleotide found in nature.

[0088] The terms “gene” or “gene fragment” are used interchangeably herein. They refer to a polynucleotide containing at least one open reading frame that is capable of encoding a particular protein after being transcribed and translated. A gene or gene fragment may be genomic or cDNA, as long as the polynucleotide contains at least one open reading frame, which may cover the entire coding region or a segment thereof. A “fusion gene” is a gene composed of at least two heterologous polynucleotides that are linked together.

[0089] A “vector” is a nucleic acid molecule, preferably self-replicating, which transfers an inserted nucleic acid molecule into and/or between host cells. The term includes vectors that function primarily for insertion of DNA or RNA into a cell, replication of vectors that function primarily for the replication of DNA or RNA, and expression vectors that function for transcription and/or translation of the DNA or RNA. Also included are vectors that provide more than one of the above functions. An “expression vector” is a polynucleotide which, when introduced into an appropriate host cell, can be transcribed and translated into a polypeptide(s). An “expression system” usually connotes a suitable host cell comprised of an expression vector that can function to yield a desired expression product.

[0090] The “target” as used in the context of MURPs is a biochemical molecule or structure to which the Binding Module or the URP-linked Binding Module can bind and where the binding event results in a desired biological activity. The target can be a protein ligand or receptor that is inhibited, activated or otherwise acted upon by the t protein. Examples of targets are hormones, cytokines, antibodies or antibody fragments, cell surface receptors, kinases, growth factors and other biochemical structures with biological activity.

[0091] A “functional module” can be any non-URP in a protein product. Thus a functional module can be a binding module (BM), an effector module (EM), a multimerization module (MM), a C-terminal module (CM), or an N-terminal module (NM). In general, functional modules are characterized by a high information content of their amino acid sequence, i.e. they contain many different amino acids and many of these amino acids are important for the function of a functional module. A functional module typically has secondary and tertiary structure, may be a folded protein domain and may contain 1, 2, 3, 4, 5 or more disulfide bonds.

[0092] The term ‘microproteins’ refers to a classification in the SCOP database. Microproteins are usually the smallest proteins with a fixed structure and typically but not exclusively have as few as 15 amino acids with two disulfides or up to 200 amino acids with more than ten disulfides. A microprotein may contain one or more microprotein domains. Some microprotein domains or domain families can have multiple more-or-less stable and multiple more or less similar structures which are conferred by different disulfide bonding patterns, so the term stable is used in a relative way to differentiate microproteins from peptides and non-microprotein domains. Most microprotein toxins are composed of a single domain, but the cell-surface receptor microproteins often have multiple domains. Microproteins can be so small because their folding is stabilized either by disulfide bonds and/or by ions such as Calcium, Magnesium, Manganese, Copper, Zinc, Iron or a variety of other multivalent ions, instead of being stabilized by the typical hydrophobic core.

[0093] The term “scaffold” refers to the minimal polypeptide ‘framework’ or ‘sequence motif’ that is used as the conserved, common sequence in the construction of protein libraries. In between the fixed or conserved residues/positions of the scaffold lie variable and hypervariable positions. A large diversity of amino acids is provided in the variable regions between the fixed scaffold residues to provide specific binding to a target molecule. A scaffold is typically defined by the conserved residues that are observed in an alignment of a family of sequence-related proteins. Fixed residues may be required for folding or structure, especially if the functions of the aligned proteins are different. A full description of a microprotein scaffold may include the number, position or spacing and bonding pattern of the cysteines, as well as position and identity of any fixed residues in the loops, including binding sites for ions such as Calcium.

[0094] The “fold” of a microprotein is largely defined by the linkage pattern of the disulfide bonds (i.e., 1-4, 2-6, 3-5). This pattern is a topological constant and is generally not amenable to conversion into another pattern without unlinking and relinking the disulfides such as by reduction and oxidation (redox agents). In general, natural proteins with related sequences adopt the same disulfide bonding patterns. The major determinants are the cysteine distance pattern (CDP) and some fixed non-cys residues, as well as a metal-binding site, if present. In few cases the folding of proteins is also influenced by the surrounding sequences (ie pro-peptides) and in some cases by chemical derivatization (ie gamma-carboxylation) of residues that allow the protein to bind divalent metal ions (ie Ca++) which assists their folding. For the vast majority of microproteins such folding help is not required.

[0095] However, proteins with the same bonding pattern may still comprise multiple folds, based on differences in the length and composition of the loops that are large enough to give the protein a rather different structure. An example are the conotoxin, cyclotoxin and anato domain families, which have the same DBP but a very different CDP and are considered to be different folds. Determinants of a protein fold are any attributes that greatly alter structure relative to a different fold, such as the number and bonding pattern of the cysteines, the spacing of the cysteines, differences in the sequence motifs of the inter-cysteine loops (especially fixed loop residues which are likely to be needed for folding, or in the location or composition of the calcium (or other metal or co-factor) binding site.

[0096] The term “disulfide bonding pattern” or “DBP” refers to the linking pattern of the cysteines, which are numbered 1-n from the N-terminus to the C-terminus of the protein. Disulfide bonding patterns are topologically constant, meaning they can only be changed by unlinking one or more disulfides such as using redox conditions. The possible 2-, 3-, and 4-disulfide bonding patterns are listed below in paragraphs 0048-0075.

[0097] The term “cysteine distance pattern” or “CDP” refers to the number of non-cysteine amino acids that separate the cysteines on a linear protein chain. Several notations are used: C5C0C3C equals C5CC3C equals CxxxxCCxxxC.

[0098] The term ‘Position n6’ or ‘n7=4’ refers to the inter-cysteine loops and ‘n6’ is defined as the loop between C6 and C7; ‘n7=4’ means the loop between C7 and C8 is 4 amino acids long, not counting the cysteines.

[0099] Serum degradation resistance—Proteins can be eliminated by degradation in the blood, which typically involves proteases in the serum or plasma. The serum degradation resistance is measured by combining the protein with human (or mouse, rat, monkey, as appropriate) serum or plasma, typically for a range of days (ie 0.25, 0.5, 1, 2, 4, 8, 16 days) at 37 C. The samples for these timepoints are then run on a western assay and the protein is detected with an antibody. The antibody can be to a tag in the protein. If the protein shows a single band on the western, where the protein’s size is identical to that of the injected protein, then no degradation has occurred. The timepoint where 50% of the protein is degraded, as judged by western, is the serum degradation half-life of the protein.

[0100] Serum protein binding—While the MURP typically has a number of modules that bind to cell-surface targets and/or serum proteins, it is desirable that the URP substantially lack unintended activities. The URP should be designed to minimize avoid interaction with (binding to) serum proteins, including antibodies. Different URP designs can be screened for serum protein binding by ELISA, immobilizing the serum proteins and then adding the URP, incubating, washing and then detecting the amount of bound URP. One approach is to detect the URP using an antibody that recognizes a tag that has been added to the URP. A different approach is to immobilize the URP (such as via a fusion to GFP) and come in with human serum, incubating, washing, and then detecting the amount of human antibodies that remain bound to the URP using secondary antibodies like goat anti-human IgG. Using these approaches we have designed our URPs to show very low levels of binding to serum proteins. However, in some applications binding to serum proteins or serum-exposed proteins is desired, for example because it can further extend the secretion half-life. In such cases one can use these same assays to design URPs that bind to serum proteins or serum-exposed proteins such as HSA or IgG. In other cases the MURP can be given binding modules that contain peptides that have been designed to bind to serum proteins or serum-exposed proteins such as HAS or IgG.

Unstructured Recombinant Polymers (URPs):

[0101] One aspect of the present invention is the design of unstructured recombinant polymers (URPs). The subject URPs are particularly useful for generating recombinant proteins of therapeutic and/or diagnostic value. The subject URPs exhibit one or more following features.

[0102] The subject URPs comprise amino acid sequences that typically share commonality with denatured peptide sequences under physiological conditions. URP sequences typically behave like denatured peptide sequences under physiological conditions. URP sequences lack well defined secondary and tertiary structures under physiological conditions. A variety of methods have been established in the art to ascertain the second and tertiary structures of a given polypeptide. For example, the secondary structure of a polypeptide can be determined by CD spectroscopy in the “far-UV” spectral region (190-250 nm). Alpha-helix, beta-sheet, and random coil structures each give rise to a characteristic shape and magnitude of CD spectra. Secondary structure can also be ascertained via certain computer programs or algorithms such as the Chou-Fasman algorithm (Chou, P. Y., et al. (1974) *Biochemistry*, 13: 222-45). For a given URP sequence, the algorithm can predict whether there exists some or no secondary structure at all. In general, URP sequences will have spectra that resemble denatured sequences due to their low degree of secondary and tertiary structure. Where desired, URP sequences can be designed to have predominantly denatured conformations under physiological conditions. URP sequences typically have a high degree of conformational flexibility under physiological conditions and they tend to have large hydrodynamic radii (Stokes’ radius) compared to globular proteins of similar molecular weight. As used herein, physiological conditions refer to a set of conditions including temperature, salt concentration, pH that mimic those conditions of a living subject. A host of physiologically relevant conditions for use in *in vitro* assays have been established. Generally, a physiological buffer contains a physiological concentration of salt and at adjusted to a neutral pH ranging from about 6.5 to about 7.8, and preferably from about 7.0 to about 7.5. A variety of physiological buffers is listed in Sambrook et al. (1989) *supra* and hence is not detailed herein. Physiologically relevant temperature ranges from about 25° C. to about 38° C., and preferably from about 30° C. to about 37° C.

[0103] The subject URPs can be sequences with low immunogenicity. Low immunogenicity can be a direct result of the conformational flexibility of URP sequences. Many antibodies recognize so-called conformational epitopes in protein antigens. Conformational epitopes are formed by regions of the protein surface that are composed of multiple discontinuous amino acid sequences of the protein antigen. The precise folding of the protein brings these sequences into a well-defined special configuration that can be recognized by antibodies. Preferred URPs are designed to avoid formation of conformational epitopes. For example, of particular interest are URP sequences having a low tendency to adapt compactly folded conformations in aqueous solution. In particular, low immunogenicity can be achieved by choosing sequences that resist antigen processing in antigen presenting cells, choosing sequences that do not bind MHC well and/or by choosing sequences that are derived from human sequences.

[0104] The subject URPs can be sequences with a high degree of protease resistance. Protease resistance can also be a result of the conformational flexibility of URP sequences. Protease resistance can be designed by avoiding known protease recognition sites. Alternatively, protease resistant sequences can be selected by phage display or related techniques from random or semi-random sequence libraries. Where desired for special applications, such as slow release from a depot protein, serum protease cleavage sites can be

built into an URP. Of particular interest are URP sequences with high stability (e.g., long serum half-life, less prone to cleavage by proteases present in bodily fluid) in blood.

[0105] The subject URP can also be characterized by the effect in that wherein upon incorporation of it into a protein, the protein exhibits a longer serum half-life and/or higher solubility as compared to the corresponding protein that is deficient in the URP. [Methods of ascertaining serum half-life are known in the art (see e.g., Alvarez, P., et al. (2004) *J Biol Chem*, 279: 3375-81). One can readily determine whether the resulting protein has a longer serum half-life as compared to the unmodified protein by practicing any methods available in the art or exemplified herein.

[0106] The subject URP can be of any length necessary to effect (a) extension of serum half-life of a protein comprising the URP; (b) an increase in solubility of the resulting protein; (c) an increased resistance to protease; and/or (d) a reduced immunogenicity of the resulting protein that comprises the URP. Typically, the subject URP has about 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 400 or more contiguous amino acids. When incorporated into a protein, the URP can be fragmented such that the resulting protein contains multiple URPs, or multiple fragments of URPs. Some or all of these individual URP sequences may be shorter than 40 amino acids as long as the combined length of all URP sequences in the resulting protein is at least 40 amino acids. Preferably, the resulting protein has a combined length of URP sequences exceeding 40, 50, 60, 70, 80, 90, 100, 150, 200 or more amino acids.

[0107] URPs may have an isoelectric point (pI) of 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5 or even 13.0.

[0108] In general, URP sequences are rich in hydrophilic amino acids and contain a low percentage of hydrophobic or aromatic amino acids. Suitable hydrophilic residues include but are not limited to glycine, serine, aspartate, glutamate, lysine, arginine, and threonine. Hydrophobic residues that are less favored in construction of URPs include tryptophan, phenylalanine, tyrosine, leucine, isoleucine, valine, and methionine. URP sequences can be rich in glycine but URP sequences can also be rich in the amino acids glutamate, aspartate, serine, threonine, alanine or proline. Thus the predominant amino acid may be G, E, D, S, T, A or P. The inclusion of proline residues tends to reduce sensitivity to proteolytic degradation.

[0109] The inclusion of hydrophilic residues typically increases URPs' solubility in water and aqueous media under physiological conditions. As a result of their amino acid composition, URP sequences have a low tendency to form aggregates in aqueous formulations and the fusion of URP sequences to other proteins or peptides tends to enhance their solubility and reduce their tendency to form aggregates, which is a separate mechanism to reduce immunogenicity.

[0110] URP sequences can be designed to avoid certain amino acids that confer undesirable properties to the protein. For instance, one can design URP sequences to contain few or none of the following amino acids: cysteine (to avoid disulfide formation and oxidation), methionine (to avoid oxidation), asparagine and glutamine (to avoid desamidation).

[0111] Glycine-Rich URPs:

[0112] In one embodiment, the subject URP comprises a glycine rich sequence (GRS). For example, glycine can be present predominantly such that it is the most prevalent residues present in the sequence of interest. In another example,

URP sequences can be designed such that glycine residues constitute at least about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100% of the total amino acids. URPs can also contain 100% glycines. In yet another example, the URPs contain at least 30% glycine and the total concentration of tryptophan, phenylalanine, tyrosine, valine, leucine, and isoleucine is less than 20%. In still another example, the URPs contain at least 40% glycine and the total concentration of tryptophan, phenylalanine, tyrosine, valine, leucine, and isoleucine is less than 10%. In still yet another example, the URPs contain at least about 50% glycine and the total concentration of tryptophan, phenylalanine, tyrosine, valine, leucine, and isoleucine is less than 5%.

[0113] The length of GRS can vary between about 5 amino acids and 200 amino acids or more. For example, the length of a single, contiguous GRS can contain 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 240, 280, 320 or 400 or more amino acids. GRS may comprise glycine residues at both ends.

[0114] GRS can also have a significant content of other amino acids, for example Ser, Thr, Ala, or Pro. GRS can contain a significant fraction of negatively charged amino acids including but not limited to Asp and Glu. GRS can contain a significant fraction of positively charged amino acids including but not limited to Arg or Lys. Where desired, URPs can be designed to contain only a single type of amino acid (i.e., Gly or Glu), sometimes only a few types of amino acid, e.g., two to five types of amino acids (e.g., selected from G, E, D, S, T, A and P), in contrast to typical proteins and typical linkers which generally are composed of most of the twenty types of amino acids. URPs may contain negatively charged residues (Asp, Glu) in 30, 25, 20, 15, 12, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 percent of the amino acids positions.

[0115] Typically, the subject GRS-containing URP has about 30, 40, 50, 60, 70, 80, 90, 100, or more contiguous amino acids. When incorporated into a protein, the URP can be fragmented such that the resulting protein contains multiple URPs, or multiple fragments of URPs. Some or all of these individual URP sequences may be shorter than 40 amino acids as long as the combined length of all URP sequences in the resulting protein is at least 30 amino acids. Preferably, the resulting protein has a combined length of URP sequences exceeding 40, 50, 60, 70, 80, 90, 100, or more amino acids.

[0116] The GRS-containing URPs are of particular interest due to, in part, the increased conformational freedom of glycine-containing peptides. Denatured peptides in solution have a high degree of conformational freedom. Most of that conformational freedom is lost upon binding of said peptides to a target like a receptor, an antibody, or a protease. This loss of entropy needs to be offset by the energy of interaction between the peptide and its target. The degree of conformational freedom of a denatured peptide is dependent on its amino acid sequences. Peptides containing many amino acids with small side chains tend to have more conformational freedom than peptides that are composed of amino acids with larger side chains. Peptides containing the amino acid glycine have particularly large degrees of freedom. It has been estimated that glycine-containing peptide bonds have about 3.4 times more entropy in solution as compared to corresponding alanine-containing sequences (D'Aquino, J. A., et al. (1996) *Proteins*, 25: 143-56). This factor increases with the number

of glycine residues in a sequence. As a result, such peptides tend to lose more entropy upon binding to targets, which reduces their overall ability to interact with other proteins as well as their ability to adopt defined three-dimensional structures. The large conformational flexibility of glycine-peptide bonds is also evident when analyzing Ramachandran plots of protein structures where glycine peptide bonds occupy areas that are rarely occupied by other peptide bonds (Venkatachalam, C. M., et al. (1969) *Annu Rev Biochem*, 38: 45-82). Stites et al. studied a database of 12,320 residues from 61 nonhomologous, high resolution crystal structures to determine the phi, psi conformational preferences of each of the 20 amino acids. The observed distributions in the native state of proteins are assumed to also reflect the distributions found in the denatured state. The distributions were used to approximate the energy surface for each residue, allowing the calculation of relative conformational entropies for each residue relative to glycine. In the most extreme case, replacement of glycine by proline, conformational entropy changes will stabilize the native state relative to the denatured state by -0.82 ± -0.08 kcal/mol at 20° C. (Stites, W. E., et al. (1995) *Proteins*, 22: 132). These observations confirm the special role of glycine among the 20 natural amino acids.

[0117] In designing the subject URPs, natural or non-natural sequences can be used. For example, a host of natural sequences containing high glycine content is provided in Table 1, Table 2, Table 3, and Table 4. One skilled in the art may adopt any one of the sequences as an URP, or modify the sequences to achieve the intended properties. Where immunogenicity to the host subject is of concern, it is preferable to design GRS-containing URPs based on glycine rich sequences derived from the host. Preferred GRS-containing URPs are sequences from human proteins or sequences that share substantial homology to the corresponding glycine rich sequences in the reference human proteins.

TABLE 1

Structural analysis of proteins that contain glycine rich sequences	
PDB file Protein function	sequences Glycine rich
1K3V Porcine Parvovirus capsid	sggggggggrgagg
1FPV Feline Panleukopenia Virus	tgsgngsggggggsgg
1IJS CpV strain D, mutant A300d	tgsgngsggggggsgg
1MVM Mvm (strain I) virus	ggsgggggsggg

TABLE 2

Open reading frames encoding GRS with 300 or more glycine residues				
Accession	Organism	Gly (%)	GRS length	Gene length Predicted Function
NP_974499	<i>Arabidopsis thaliana</i>	64	509	579 unknown
ZP_00458077	<i>Burkholderia cenocopacia</i>	66	373	518 putative lipoprotein
XP_477841	<i>Oryza sativa</i>	74	371	422 unknown
NP_910409	<i>Oryza sativa</i>	75	368	400 putative cell-wall precursor
NP_610660	<i>Drosophila melanogaster</i>	66	322	610 transposable element

TABLE 3

Examples of human GRS					
Accession	Gly (%)	GRS length	Gene length	Hydro- phobics	Predicted Function
NP_000217	62	135	622	yes	keratin 9
NP_631961	61	73	592	yes	TBP-associated factor 15 isoform 1
NP_476429	65	70	629	yes	keratin 3
NP_000418	70	66	316	yes	loricrin, cell envelope
NP_056932	60	66	638	yes	cytokeratin 2

TABLE 4

Additional examples of human GRS		
Accession	Sequences	Number of amino acids
NP_006228	GPGGGGPGGGGPGGGGPGGGGGGGP GGGGGPGGG	37
NP_787059	GAGGGGGGGGGGGSGGGGGGGGAGA GGAGAG	33
NP_009060	GGGSGSGGAGGGSGGSGSGGGGGAG GGGG	32
NP_031393	GDGGGAGGGGGGGSGGGSGGGGGG	27
NP_005850	GSGSGSGGGGGGGGGSGGGGGG	25
NP_061856	GGGRGGRGGGRGGGRGGGRGGG	22
NP_787059	GAGGGGGGGGGGGSGGGGGGGGAGA GGAGAG	33
NP_009060	GGGSGSGGAGGGSGGSGSGGGGGAG GGGG	32
NP_031393	GDGGGAGGGGGGGSGGGSGGGGGG	27
NP_115818	GSGSGSGSGGGPGPGPGGGGG	21
XP_376532	GEGGGGGGEGGGAGGGSG	18
NP_065104	GGGGGGGDGGG	12
	GGGSGSGGAGGGSGGGSGSGGGGGAGGGGGSSGGSGTAGGHS	
	POU domain, class 4, transcription factor 1 [Homo sapiens] GPGGGGGPGGGGPGGGGPGGGGGPGGGGGPGGG	
	YEATS domain containing 2 [Homo sapiens] GGSGAGGGGGGGGGSGSGGGGSTGGGGTAGGG	

TABLE 4-continued

<u>Additional examples of human GRS</u>		
Accession	Sequences	Number of amino acids
	AT rich interactive domain 1B (SWI1-like) isoform 3; BRG1-binding protein ELD/OSA1; Eld (eyelid)/Osa protein [<i>Homo sapiens</i>] <u>GAGGGGGGGGGGGGGGGGGGGGGAGAGGAGAG</u>	
	AT rich interactive domain 1B (SWI1-like) isoform 2; BRG1-binding protein ELD/OSA1; Eld (eyelid)/Osa protein [<i>Homo sapiens</i>] <u>GAGGGGGGGGGGGGGGGGGGGGGAGAGGAGAG</u>	
	AT rich interactive domain 1B (SWI1-like) isoform 1; BRG1-binding protein ELD/OSA1; Eld (eyelid)/Osa protein [<i>Homo sapiens</i>] <u>GAGGGGGGGGGGGGGGGGGGGGGAGAGGAGAG</u>	
	purine-rich element binding protein A; purine-rich single-stranded DNA-binding protein alpha; transcriptional activator protein PUR-alpha [<i>Homo sapiens</i>] <u>GHPGSGSGSGGGGGGGGGGGGGGGGGGGAPGG</u>	
	regulatory factor X1; trans-acting regulatory factor 1; enhancer factor C; MHC class II regulatory factor RFX [<i>Homo sapiens</i>] <u>GGGGSGGGGGGGGGGGGGGGSTGGGSGAG</u>	
	bromo domain-containing protein disrupted in leukemia [<i>Homo sapiens</i>] <u>GGRGRGGRGRGSRGRGGGGTRGRGRGRGGRG</u>	
	unknown protein [<i>Homo sapiens</i>] <u>GSGGSGSGSGGGPGPGPGGGGGPSGSGSGPG</u>	
	PREDICTED: hypothetical protein XP_059256 [<i>Homo sapiens</i>] <u>GGGGGGGGGGGGGGGGGGGGGGGGGGGGGG</u>	
	zinc finger protein 281; ZNP-99 transcription factor [<i>Homo sapiens</i>] <u>GGGGTGSSGGSGSGGGSGGGGGGGSSG</u>	
	RNA binding protein (autoantigenic, hnRNP-associated with lethal yellow) short isoform; RNA-binding protein (autoantigenic); RNA-binding protein (autoantigenic, hnRNP-associated with lethal yellow) [<i>Homo sapiens</i>] <u>GDGGGAGGGGGGGGGGGGGGGGGGGGG</u>	
	signal recognition particle 68kDa [<i>Homo sapiens</i>] <u>GGGGGGGGGGGGGGGGGGGGGGGGGAGG</u>	
	KIAA0265 protein [<i>Homo sapiens</i>] <u>GGGAAGAGGGGSGAGGGSGGSGGGRGTG</u>	
	engrailed homolog 2; Engrailed-2 [<i>Homo sapiens</i>] <u>GAGGGRGGGAGGEGGASGAEGGGGAGG</u>	
	RNA binding protein (autoantigenic, hnRNP-associated with lethal yellow) long isoform; RNA-binding protein (autoantigenic); RNA-binding protein (autoantigenic, hnRNP-associated with lethal yellow) [<i>Homo sapiens</i>] <u>GDGGGAGGGGGGGGGGGGGGGGGGGGG</u>	
	androgen receptor; dihydrotestosterone receptor [<i>Homo sapiens</i>] <u>GGGGGGGGGGGGGGGGGGGGGGGAG</u>	

TABLE 4-continued

<u>Additional examples of human GRS</u>		
Accession	Sequences	Number of amino acids
	homeo box D11; homeo box 4F; Hox-4.6, mouse, homolog of; homeobox protein Hox-D11 [<i>Homo sapiens</i>] <u>GGGGGGGAGGGSSGGGPGGGGGGAGG</u>	
	frizzled 8; frizzled (<i>Drosophila</i>) homolog 8 [<i>Homo sapiens</i>] <u>GGGGGPGGGGGGGGGGGGGGGGGGG</u>	
	ocular development-associated gene [<i>Homo sapiens</i>] <u>GRGGAGSGGAGSGAAGGTGSSGGGG</u>	
	homeo box B3; homeo box 2G; homeobox protein Hox-B3 [<i>Homo sapiens</i>] <u>GGGGGGGGGGGGGGGGGGGGGGGGGG</u>	
	chromosome 2 open reading frame 29 [<i>Homo sapiens</i>] <u>GGSGGGRRGGASGPGSGSGGPGGPAG</u>	
	DKFZP564F0522 protein [<i>Homo sapiens</i>] <u>GGHHGDRGGGRGGGRGGGRGGGRAG</u>	
	PREDICTED: similar to Homeobox even-skipped homolog protein 2 (EVX-2) [<i>Homo sapiens</i>] <u>GSRGGGGGGGGGGGGGGGGGGAGAGGG</u>	
	ras homolog gene family, member U; Ryu GTPase; Wnt-1 responsive Cdc42 homolog; 2310026M05Rik; GTP-binding protein like 1; CDC42-like GTPase [<i>Homo sapiens</i>] <u>GGRGGRGPGEPPGGRGRAGGAEGRG</u>	
	scratch 2 protein; transcriptional repressor scratch 2; scratch (<i>drosophila</i> homolog) 2, zinc finger protein [<i>Homo sapiens</i>] <u>GGGGGDAGGSGDAGGAGGRAGAG</u>	
	nucleolar protein family A, member 1; GAR1 protein [<i>Homo sapiens</i>] <u>GGGRGGRRGGGGGGGGGGGGGGGGGG</u>	
	keratin 1; Keratin-1; cytokeratin 1; hair alpha protein [<i>Homo sapiens</i>] <u>GGSGGGGGGSSGGRGSGGGSSGG</u>	
	hypothetical protein FLJ31413 [<i>Homo sapiens</i>] <u>GSGPGTGGGGSGSGGGGGGGGGGG</u>	
	one cut domain, family member 2; onecut 2 [<i>Homo sapiens</i>] <u>GARGGGSGGGGGGGGGGGGGGGGPG</u>	
	POU domain, class 3, transcription factor 2 [<i>Homo sapiens</i>] <u>GGGGGGGGGGGGGGGGGGGGGGGGGG</u>	
	PREDICTED: similar to THO complex subunit 4 (Tho4) (RNA and export factor binding protein 1) (REF 1-I) (Ally of AML-1 and LEF-1) (Aly/REF) [<i>Homo sapiens</i>] <u>GGTRGGTRGGTRGGDRGRGRGAG</u>	
	PREDICTED: similar to THO complex subunit 4 (Tho4) (RNA and export factor binding protein 1) (REF 1-I) (Ally of AML-1 and LEF-1) (Aly/REF) [<i>Homo sapiens</i>] <u>GGTRGGTRGGTRGGDRGRGRGAG</u>	
	POU domain, class 3, transcription factor 3 [<i>Homo sapiens</i>] <u>GAGGGGGGGGGGGGGGGGGGGGGGG</u>	

TABLE 4-continued

<u>Additional examples of human GRS</u>		Number of
Accession	Sequences	amino acids
	nucleolar protein family A, member 1; GAR1 protein [<i>Homo sapiens</i>] <u>GGGRGGRRGGGRGGGRGGGRGGG</u>	
	fibrillarin; 34-kD nucleolar scleroderma antigen; RNA, U3 small nucleolar interacting protein 1 [<i>Homo sapiens</i>] <u>GRGRGGGGGGGGGGGGGGGGGG</u>	
	zinc finger protein 579 [<i>Homo sapiens</i>] <u>GRGRGRGRGRGRGRGRGRGGAG</u>	
	calpain, small subunit 1; calcium-activated neutral proteinase; calpain, small polypeptide; calpain 4, small subunit (30K); calcium-dependent protease, small subunit [<i>Homo sapiens</i>] <u>GAGGGGGGGGGGGGGGGGGGGGG</u>	
	keratin 9 [<i>Homo sapiens</i>] <u>GGGSGGGHSGGSGGGHSGGSGG</u>	
	forkhead box D1; forkhead-related activator 4; Forkhead, <i>Drosophila</i> , homolog-like 8; forkhead (<i>Drosophila</i>)-like 8 [<i>Homo sapiens</i>] <u>GAGAGGGGGGGAGGGGSAGSG</u>	
	PREDICTED: similar to RIKEN cDNA C230094B15 [<i>Homo sapiens</i>] <u>GGPGTGSGGGGAGTGGGAGGPG</u>	
	<u>GGGGGGGGGAGGAGGAGSAGGG</u>	
	cadherin 22 precursor; ortholog of rat PB-cadherin [<i>Homo sapiens</i>] <u>GGDGGGSAGGGAGGGSGGGAG</u>	
	AT-binding transcription factor 1; AT motif- binding factor 1 [<i>Homo sapiens</i>] <u>GGGGGGSGGGGGGGGGGGGGG</u>	
	eomesodermin; t box, brain, 2; eomesodermin (<i>Xenopus laevis</i>) homolog [<i>Homo sapiens</i>] <u>GPGAGAGSGAGGSSGGGGGPG</u>	
	phosphatidylinositol transfer protein, membrane- associated 2; PYK2 N-terminal domain-interacting receptor 3; retinal degeneration B alpha 2 (<i>Drosophila</i>) [<i>Homo sapiens</i>] <u>GGGGGGGGGGSSGGGSSGG</u>	
	sperm associated antigen 8 isoform 2; sperm membrane protein 1 [<i>Homo sapiens</i>] <u>GS SGSGPGSGPGSGPGSGPGSG</u>	
	PREDICTED: RNA binding motif protein 27 [<i>Homo sapiens</i>] <u>GPGPGPGPGPGPGPGPGPGPG</u>	
	AP1 gamma subunit binding protein 1 isoform 1; gamma-synergin; adaptor-related protein complex 1 gamma subunit-binding protein 1 [<i>Homo sapiens</i>] <u>GAGSGGGGAAGAGAGSAGGGG</u>	
	AP1 gamma subunit binding protein 1 isoform 2; gamma-synergin; adaptor-related protein complex 1 gamma subunit-binding protein 1 [<i>Homo sapiens</i>] <u>GAGSGGGGAAGAGAGSAGGGG</u>	

TABLE 4-continued

<u>Additional examples of human GRS</u>		Number of
Accession	Sequences	amino acids
	ankyrin repeat and sterile alpha motif domain containing 1; ankyrin repeat and SAM domain containing 1 [<i>Homo sapiens</i>] <u>GGGGGGSGGGGGSGGGGGG</u>	
	methyl-CpG binding domain protein 2 isoform 1 [<i>Homo sapiens</i>] <u>GRGRGRGRGRGRGRGRGRGRG</u>	
	triple functional domain (PTPRF interacting) [<i>Homo sapiens</i>] <u>GGGGGGSGSGGGGGSGGGG</u>	
	forkhead box D3 [<i>Homo sapiens</i>] <u>GGEEGGASGGGPGAGSGSAGG</u>	
	sperm associated antigen 8 isoform 1; sperm membrane protein 1 [<i>Homo sapiens</i>] <u>GS SGSGPGSGPGSGPGSGPGSG</u>	
	methyl-CpG binding domain protein 2 testis- specific isoform [<i>Homo sapiens</i>] <u>GRGRGRGRGRGRGRGRGRGRG</u>	
	cell death regulator aven; programmed cell death 12 [<i>Homo sapiens</i>] <u>GGGGGGGGDGGRRGRGRGRG</u>	
	regulator of nonsense transcripts 1; delta helicase; up-frameshift mutation 1 homolog (<i>S. cerevisiae</i>); nonsense mRNA reducing factor 1; yeast Upflp homolog [<i>Homo sapiens</i>] <u>GGPGGPGGGGAGGPGGAGAG</u>	
	small conductance calcium-activated potassium channel protein 2 isoform a; apamin-sensitive small-conductance Ca2+-activated potassium channel [<i>Homo sapiens</i>] <u>GTGGGGSTGGGGGGSGHG</u>	
	SRY (sex determining region Y)-box 1; SRY-related HMG-box gene 1 [<i>Homo sapiens</i>] <u>GPAGAGGGGGGGGGGGGGG</u>	
	transcription factor 20 isoform 2; stromelysin-1 platelet-derived growth factor-responsive element binding protein; stromelysin 1 PDGF-responsive element-binding protein; SPRE-binding protein; nuclear factor SPBP [<i>Homo sapiens</i>] <u>GGTGGSSGSSGSGSGGRRG</u>	
	transcription factor 20 isoform 1; stromelysin-1 platelet-derived growth factor-responsive element binding protein; stromelysin 1 PDGF-responsive element-binding protein; SPRE-binding protein; nuclear factor SPBP [<i>Homo sapiens</i>] <u>GGTGGSSGSSGSGSGGRRG</u>	
	Ras-interacting protein 1 [<i>Homo sapiens</i>] <u>GS GTGTTGSSGAGGPGTPGG</u>	
	BMP-2 inducible kinase isoform b [<i>Homo sapiens</i>] <u>GGSGGGAAGGAGGAGAGAG</u>	
	BMP-2 inducible kinase isoform a [<i>Homo sapiens</i>] <u>GGSGGGAAGGAGGAGAGAG</u>	
	forkhead box C1; forkhead-related activator 3; Forkhead, <i>Drosophila</i> , homolog-like 7; forkhead	

TABLE 4-continued

<u>Additional examples of human GRS</u>	
Accession	Sequences
	Number of amino acids
	(<i>Drosophila</i>)-like 7; iridogoniodysgenesis type 1 [<i>Homo sapiens</i>] <u>GSSGGGGGAGAGGAGAGG</u>
	splicing factor p54; arginine-rich 54 kDa nuclear protein [<i>Homo sapiens</i>] <u>GPGPSGGPGGGGGGGGGGG</u>
	v-maf musculoaponeurotic fibrosarcoma oncogene homolog; Avian musculoaponeurotic fibrosarcoma (MAF) protooncogene; v-maf musculoaponeurotic fibrosarcoma (avian) oncogene homolog [<i>Homo sapiens</i>] <u>GGGGGGGGGGGGGAAGAGG</u>
	small nuclear ribonucleoprotein D1 polypeptide 16kDa; snRNP core protein D1; Sm-D autoantigen; small nuclear ribonucleoprotein D1 polypeptide (16kD) [<i>Homo sapiens</i>] <u>GRGRGRGRGRGRGRGRGR</u>
	hypothetical protein H41 [<i>Homo sapiens</i>] <u>GSAGSSGAAGAGGGAGAG</u>

URPs Containing Non-Glycine Residues (NGR):

[0118] The sequences of non-glycine residues in these GRS can be selected to optimize the properties of URPs and hence the proteins that contain the desired URPs. For instance, one can optimize the sequences of URPs to enhance the selectivity of the resulting protein for a particular tissue, specific cell type or cell lineage. For example, one can incorporate protein sequences that are not ubiquitously expressed, but rather are differentially expressed in one or more of the body tissues including heart, liver, prostate, lung, kidney, bone marrow, blood, skin, bladder, brain, muscles, nerves, and selected tissues that are affected by diseases such as infectious diseases, autoimmune disease, renal, neuronal, cardiac disorders and cancers. One can employ sequences representative of a specific developmental origin, such as those expressed in an embryo or an adult, during ectoderm, endoderm or mesoderm formation in a multi-cellular organism. One can also utilize sequence involved in a specific biological process, including but not limited to cell cycle regulation, cell differentiation, apoptosis, chemotaxis, cell motility and cytoskeletal rearrangement. One can also utilize other non-ubiquitously expressed protein sequences to direct the resulting protein to a specific subcellular locations: extracellular matrix, nucleus, cytoplasm, cytoskeleton, plasma and/or intracellular membranous structures which include but are not limited to coated pits, Golgi apparatus, endoplasmic reticulum, endosome, lysosome, and mitochondria.

[0119] A variety of these tissue-specific, cell-type specific, subcellular location specific sequences are known and available from numerous protein databases. Such selective URP sequences can be obtained by generating libraries of random or semi-random URP sequences, injecting them into animals or patients, and determining sequences with the desired tissue selectivity in tissue samples. Sequence determination can be performed by mass spectrometry. Using similar methods one

can select URP sequences that facilitate oral, buccal, intestinal, nasal, thecal, peritoneal, pulmonary, rectal, or dermal uptake.

[0120] Of particular interest are URP sequences that contain regions that are relatively rich in the positively charged amino acids arginine or lysine which favor cellular uptake or transport through membranes. URP sequences can be designed to contain one or several protease-sensitive sequences. Such URP sequences can be cleaved once the product of the invention has reached its target location. This cleavage may trigger an increase in potency of the pharmaceutically active domain (pro-drug activation) or it may enhance binding of the cleavage product to a receptor. URP sequences can be designed to carry excess negative charges by introducing aspartic acid or glutamic acid residues. Of particular interest are URP that contain great than 5%, greater than 6%, 7%, 8%, 9%, 10%, 15%, 30% or more glutamic acid and less than 2% lysine or arginine. Such URPs carry an excess negative charge and as a result they have a tendency to adopt open conformations due to electrostatic repulsion between individual negative charges of the peptide. Such an excess negative charge leads to an effective increase in their hydrodynamic radius and as a result it can lead to reduced kidney clearance of such molecules. Thus, one can modulate the effective net charge and hydrodynamic radius of a URP sequence by controlling the frequency and distribution of negatively charged amino acids in the URP sequences. Most tissues and surfaces in a human or animal carry excess negative charges. By designing URP sequences to carry excess negative charges one can minimize non-specific interactions between the resulting protein comprising the URP and various surfaces such as blood vessels, healthy tissues, or various receptors.

[0121] URPs may have a repetitive amino acid sequence of the format (Motif)_x in which a sequence motif forms a direct repeat (ie ABCABCABCABC) or an inverted repeat (ABC-CBAABCCBA) and the number of these repeats can be 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 35, 40, 50 or more. URPs or the repeats inside URPs often contain only 1, 2, 3, 4, 5 or 6 different types of amino acids. URPs typically consist of repeats of human amino acid sequences that are 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 26, 28, 30, 32, 34, 36 or more amino acids long, but URPs may also consist of non-human amino acid sequences that are 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50 amino acids long.

[0122] URPs Derived from Human Sequences:

[0123] URPs can be derived from human sequences. The human genome contains many subsequences that are rich in one particular amino acid. Of particular interest are such amino acid sequences that are rich in a hydrophilic amino acid like serine, threonine, glutamate, aspartate, or glycine. Of particular interest are such subsequences that contain few hydrophobic amino acids. Such subsequences are predicted to be unstructured and highly soluble in aqueous solution. Such human subsequences can be modified to further improve their utility. FIG. 17 shows an exemplary human sequence that is rich in serine and that can be isolated as the subject URP. The exemplified dentin sialophosphoprotein contains a 670-amino acid subsequence in which 64% of the residues are serine and most other positions are hydrophilic amino acids such as aspartate, asparagines, and glutamate. The sequence is extremely repetitive and as a result it has a low information content. One can directly use subsequences

of such a human protein. Where desired, one can modify the sequence in a way that preserves its overall character but which makes it more suitable for pharmaceutical applications. Examples of sequences that are related to dentin sialophosphoprotein are (SSD)_n, (SSDSSN)_n, (SSE)_n, where n is between about 4 and 200.

[0124] The use of sequences from human proteins is particularly desirable in design of URPs with reduced immunogenicity in a human subject. A key step for eliciting an immune response to a foreign protein is the presentation of peptide fragments of said protein by MHC class II receptors. These MHCII-bound fragments can then be detected by T cell receptors, which triggers the proliferation of T helper cells and initiates an immune response. The elimination of T cell epitopes from pharmaceutical proteins has been recognized as a means to reduce the risk of eliciting an immune reaction (Stickler, M., et al. (2003) *J Immunol Methods*, 281: 95-108). MHCII receptors typically interact with an epitope having e.g., a 9-amino acid long region of the displayed peptides. Thus, one can reduce the risk of eliciting an immune response to a protein in patients if all or most of the possible 9mer subsequences of the protein can be found in human proteins and if so, these sequences and repeats of these sequences will not be recognized by the patient as foreign sequences. One can incorporate human sequences into the design of URP sequences by oligomerizing or concatenating human sequences that have suitable amino acid compositions. These can be direct repeats or inverted repeats or mixtures of different repeats. For instance one can oligomerize the sequences shown in table 2. Such oligomers have reduced risk of being immunogenic. However, the junction sequences between the monomer units can still contain T cell epitopes that can trigger an immune reaction, which is illustrated in FIG. 3. One can further reduce the risk of eliciting an immune response by designing URP sequences based on multiple overlapping human sequences. This approach is illustrated in FIG. 4. The URP sequence in FIG. 2 designed as an oligomer based on multiple human sequences such that each 9mer subsequences of the oligomer can be found in a human protein. In these designs, every 9-mer subsequence is a human sequence. An example of a URP sequence based on three human sequences is shown in FIG. 5. It is also possible to design URP sequences based on a single human sequences such that all possible 9mer subsequences in the oligomeric URP sequences occur in the same human protein. An example is shown in FIG. 6 based on the POU domain that is rich in glycine and proline. The repeating monomer in the URP sequence is only a fragment of the human protein and its flanking sequences is identical to the repeating unit as illustrated in FIG. 6. Non-oligomeric URP sequences can be designed based on human proteins as well. The primary conditions are that all 9mer sub-sequences can be found in human sequences. The amino acid composition of the sequences preferably contains few hydrophobic residues. Of particular interest are URP sequences that are designed based on human sequences and that contain a large fraction of glycine residues.

[0125] Utilizing this or similar scheme, one can design a class of URPs that comprise repeat sequences with low immunogenicity to the host of interest. Host of interest can be any animals, including vertebrates and invertebrates. Preferred hosts are mammals such as primates (e.g. chimpanzees and humans), cetaceans (e.g. whales and dolphins), chiropterans (e.g. bats), perrisodactyls (e.g. horses and rhinoceroses), rodents (e.g. rats), and certain kinds of insectivores such as

shrews, moles and hedgehogs. Where human is selected as the host, the URPs typically contain multiple copies of the repeat sequences or units, wherein the majority of segments comprising about 6 to about 15 contiguous amino acids are present in one or more native human proteins. One can also design URPs in which the majority of segments comprising between about 9 to about 15 contiguous amino acids are found in one or more native human proteins. As used herein, majority of the segments refers to more than about 50%, preferably 60%, preferably 70%, preferably 80%, preferably 90%, preferably 100%. Where desired, each of the possible segments between about 6 to 15 amino acids, preferably between about 9 to 15 amino acids within the repeating units are present in one or more native human proteins. The URPs can comprise multiple repeating units or sequences, for example having 2, 3, 4, 5, 6, 7, 8, 9, 10, or more repeating units.

[0126] Design of URPs that are Substantially Free of Human T-Cell Epitopes:

[0127] URP sequences can be designed to be substantially free of epitopes recognized by human T cells. For instance, one can synthesize a series of semi-random sequences with amino acid compositions that favor denatured, unstructured conformations and evaluate these sequences for the presence of human T cell epitopes and whether they are human sequences. Assays for human T cell epitopes have been described (Stickler, M., et al. (2003) *J Immunol Methods*, 281: 95-108). Of particular interest are peptide sequences that can be oligomerized without generating T cell epitopes or non-human sequences. This can be achieved by testing direct repeats of these sequences for the presence of T-cell epitopes and for the occurrence of 6 to 15-mer and in particular 9-mer subsequences that are not human. An alternative is to evaluate multiple peptide sequences that can be assembled into repeating units as described in the previous section for the assembly of human sequences. Another alternative is to design URP sequences that result in low scores using epitope prediction algorithms like TEPITOPE (Sturmliolo, T., et al. (1999) *Nat Biotechnol*, 17: 555-61). Another approach to avoiding T-cell epitopes is to avoid amino acids that can serve as anchor residues during peptide display on MHC, such as M, I, L, V, F. Hydrophobic amino acids and positively charged amino acids can frequently serve as such anchor residues and minimizing their frequency in a URP sequences reduces the chance of generating T-cell epitopes and thus eliciting an immune reaction. The selected URPs generally contain sub-sequences that are found in at least one human protein, and have a lower content of hydrophobic amino acids.

[0128] URP sequences can be designed to optimize protein production. This can be achieved by avoiding or minimizing repetitiveness of the encoding DNA. URP sequences such as poly-glycine may have very desirable pharmaceutical properties but their manufacturing can be difficult due to the high GC-content of DNA sequences encoding for GRS and due to the presence of repeating DNA sequences that can lead to recombination.

[0129] As noted above, URP sequences can be designed to be highly repetitive at the amino acid level. As a result the URP sequences have very low information content and the risk of eliciting an immune reaction can be reduced.

[0130] Non-limiting examples of URPs containing repeating amino acids are: poly-glycine, poly-glutamic acid, poly-aspartic acid, poly-serine, poly-threonine, (GX)_n, where G is glycine and X is serine, aspartic acid, glutamic acid, threo-

nine, or proline and n is at least 20, (GGX)_n, where X is serine, aspartic acid, glutamic acid, threonine, or proline and n is at least 13, (GGGX)_n, where X is serine, aspartic acid, glutamic acid, threonine, or proline and n is at least 10, (GGGGX)_n, where X is serine, aspartic acid, glutamic acid, threonine, or proline and n is at least 8, (G_zX)_n, where X is serine, aspartic acid, glutamic acid, threonine, or proline, n is at least 15, and z is between 1 and 20.

[0131] The number of these repeats can be any number between 10 and 100. Products of the invention may contain URP sequences that are semi-random sequences. Examples are semi-random sequences containing at least 30, 40, 50, 60 or 70% glycine in which the glycines are well dispersed and in which the total concentration of tryptophan, phenylalanine, tyrosine, valine, leucine, and isoleucine is less than 70, 60, 50, 40, 30, 20, or 10% when combined. A preferred semi-random URP sequence contains at least 40% glycine and the total concentration of tryptophan, phenylalanine, tyrosine, valine, leucine, and isoleucine is less than 10%. A more preferred random URP sequence contains at least 50% glycine and the total concentration of tryptophan, phenylalanine, tyrosine, valine, leucine, and isoleucine is less than 5%. URP sequences can be designed by combining the sequences of two or more shorter URP sequences or fragments of URP sequences. Such a combination allows one to better modulate the pharmaceutical properties of the product containing the URP sequences and it allows one to reduce the repetitiveness of the DNA sequences encoding the URP sequences, which can improve expression and reduce recombination of the URP encoding sequences.

[0132] URP sequences can be designed and selected to possess several of the following desired properties: a) high genetic stability of the coding sequences in the production host, b) high level of expression, c) low (predicted/calculated) immunogenicity, d) high stability in presence of serum proteases and/or other tissue proteases, e) large hydrodynamic radius under physiological conditions. One exemplary approach to obtain URP sequences that meet multiple criteria is to construct a library of candidate sequences and to identify from the library the suitable subsequences. Libraries can comprise random and/or semi-random sequences. Of particular utility are codon libraries, which is a library of DNA molecules that contains multiple codons for the identical amino acid residue. Codon randomization can be applied to selected amino acid positions of a certain type or to most or all positions. True codon libraries encode only a single amino acid sequence, but they can easily be combined with amino acid libraries, which is a population of DNA molecules encoding a mixture of (related or unrelated) amino acids at the same residue position. Codon libraries allow the identification of genes that have relatively low repetitiveness at the DNA level but that encode highly repetitive amino acid sequences. This is useful because repetitive DNA sequences tend to recombine, leading to instability. One can also construct codon libraries that encode limited amino acid diversity. Such libraries allow introduction of a limited number of amino acids in some positions of the sequence while other positions allow for codon variation but all codons encode the same amino acid. One can synthesize partially random oligonucleotides by incorporating mixtures of nucleotides at the same position during oligonucleotide synthesis. Such partially random oligonucleotides can be fused by overlap PCR or ligation-based approaches. In particular, one can multimerize semi-random oligonucleotides that encode glycine-rich

sequences. These oligonucleotides can differ in length and sequences and codon usage. As a result, one obtains a library of candidate URP sequences. Another method to generate libraries is to synthesize a starting sequence and subsequently subject said sequence to partial randomization. This can be done by cultivation of the gene encoding the URP sequences in a mutator strain or by amplification of the encoding gene under mutagenic conditions (Leung, D., et al. (1989) *Technique*, 1: 11-15). URP sequences with desirable properties can be identified from libraries using a variety of methods. Sequences that have a high degree of genetic stability can be enriched by cultivating the library in a production host. Sequences that are unstable will accumulate mutations, which can be identified by DNA sequencing. Variants of URP sequences that can be expressed at high level can be identified by screening or selection using multiple protocols known to someone skilled in the art. For instance one can cultivate multiple isolates from a library and compare expression levels. Expression levels can be measured by gel analysis, analytical chromatography, or various ELISA-based methods. The determination of expression levels of individual sequence variants can be facilitated by fusing the library of candidate URP sequences to sequence tags like myc-tag, His-tag, HA-tag. Another approach is to fuse the library to an enzyme or other reporter protein like green fluorescent protein. Of particular interest is the fusion of the library to a selectable marker like beta-lactamase or kanamycin-acyl transferase. One can use antibiotic selection to enrich for variants with high level of expression and good genetic stability. Variants with good protease resistance can be identified by screening for intact sequences after incubation with proteases. An effective way to identify protease-resistant URP sequences is bacterial phage display or related display methods. Multiple systems have been described where sequences that undergo rapid proteolysis can be enriched by phage display. These methods can be easily adopted to enrich for protease resistant sequences. For example, one can clone a library of candidate URP sequences between an affinity tag and the pIII protein of M13 phage. The library can then be exposed to proteases or protease-containing biological samples like blood or lysosomal preparations. Phage that contain protease-resistant sequences can be captured after protease treatment by binding to the affinity tag. Sequences that resist degradation by lysosomal preparations are of particular interest because lysosomal degradation is a key step during antigen presentation in dendritic and other antigen presenting cells. Phage display can be utilized to identify candidate URP sequences that do not bind to a particular immune serum in order to identify URP sequences with low immunogenicity. One can immunize animals with a candidate URP sequence or with a library of URP sequences to raise antibodies against the URP sequences in the library. The resulting serum can then be used for phage panning to remove or identify sequences that are recognized by antibodies in the resulting immune serum. Other methods like bacterial display, yeast display, ribosomal display can be utilized to identify variants of URP sequences with desirable properties. Another approach is the identification of URP sequences of interest by mass spectrometry. For instance, one can incubate a library of candidate URP sequences with a protease or biological sample of interest and identify sequences that resist degradation by mass spectrometry. In a similar approach one can identify URP sequences that facilitate oral uptake. One can feed a mixture of candidate URP sequences

to animals or humans and identify variants with the highest transfer or uptake efficiency across some tissue barrier (ie dermal, etc) by mass spectrometry. In a similar way, one can identify URP sequences that favor other uptake mechanisms like pulmonary, intranasal, rectal, transdermal delivery. One can also identify URP sequences that favor cellular uptake or URP sequences that resist cellular uptake.

[0133] URP sequences can be designed by combining URP sequences or fragments of URP sequences that were designed by any of the methods described above. In addition, one can apply semi-random approaches to optimize sequences that were designed based on the rules described above. Of particular interest is codon optimization with the goal of improving expression of the enhanced proteins and to improve the genetic stability of the encoding gene in the production hosts. Codon optimization is of particular importance for URP sequences that are rich in glycine or that have very repetitive amino acid sequences. Codon optimization can be performed using computer programs (Gustafsson, C., et al. (2004) *Trends Biotechnol.*, 22: 346-53), some of which minimize ribosomal pausing (Coda Genomics Inc.). When designing URP sequences one can consider a number of properties. One can minimize the repetitiveness in the encoding DNA sequences. In addition, one can avoid or minimize the use of codons that are rarely used by the production host (ie the AGG and AGA arginine codons and one Leucine codon in *E. coli*) DNA sequences that have a high level of glycine tend to have a high GC content that can lead to instability or low expression levels. Thus, when possible it is preferred to choose codons such that the GC-content of URP-encoding sequence is suitable for the production organism that will be used to manufacture the URP.

[0134] URP encoding genes can be made in one or more steps, either fully synthetically or by synthesis combined with enzymatic processes, such as restriction enzyme-mediated cloning, PCR and overlap extension. URP modules can be constructed such that the URP module-encoding gene has low repetitiveness while the encoded amino acid sequence has a high degree of repetitiveness. The approach is illustrated in FIG. 11. As a first step, one constructs a library of relatively short URP sequences. This can be a pure codon library such that each library member has the same amino acid sequence but many different coding sequences are possible. To facilitate the identification of well-expressing library members one can construct the library as fusion to a reporter protein. Examples of suitable reporter genes are green fluorescent protein, luciferase, alkaline phosphatase; beta-galactosidase. By screening one can identify short URP sequences that can be expressed in high concentration in the host organism of choice. Subsequently, one can generate a library of random URP dimers and repeat the screen for high level of expression. Dimerization can be performed by ligation, overlap extension or similar cloning techniques. This process of dimerization and subsequent screening can be repeated multiple times until the resulting URP sequence has reached the desired length. Optionally, one can sequence clones in the library to eliminate isolates that contain undesirable sequences. The initial library of short URP sequences can allow some variation in amino acid sequence. For instance one can randomize some codons such that a number of hydrophilic amino acids can occur in said position. During the process of iterative multimerization one can screen library members for other characteristics like solubility or protease resistance in addition to a screen for high-level expression.

Instead of dimerizing URP sequences one can also generate longer multimers. This allows one to faster increase the length of URP modules.

[0135] Many URP sequences contain particular amino acids at high fraction. Such sequences can be difficult to produce by recombinant techniques as their coding genes can contain repetitive sequences that are subject to recombination. Furthermore, genes that contain particular codons at very high frequencies can limit expression as the respective loaded tRNAs in the production host become limiting. An example is the recombinant production of GRS. Glycine residues are encoded by 4 triplets, GGG, GGC, GGA, and GGT. As a result, genes encoding GRS tend to have high GC-content and tend to be particularly repetitive. An additional challenge can result from codon bias of the production host. In the case of *E. coli*, two glycine codons, GGA and GGG, are rarely used in highly expressed proteins. Thus codon optimization of the gene encoding URP sequences can be very desirable. One can optimize codon usage by employing computer programs that consider codon bias of the production host (Gustafsson, C., et al. (2004) *Trends Biotechnol.*, 22: 346-53). As an alternative, one can construct codon libraries where all members of the library encode the same amino acid sequence but where codon usage is varied. Such libraries can be screened for highly expressing and genetically stable members which are particularly suitable for the large-scale production of URP-containing products.

Multivalent Unstructured Recombinant Proteins (MURPs):

[0136] As noted above, the subject URPs are particularly useful as modules for design of proteins of therapeutic value. Accordingly, the present invention provides proteins comprising one or more subject URPs. Such proteins are termed herein Multivalent Unstructured Recombinant Proteins (MURPs).

[0137] To construct MURPs, one or more URP sequences can be fused to the N-terminus or C-terminus of a protein or inserted in the middle of the protein, e.g., into loops of a protein or in between modules of the protein of interest, to give the resulting modified protein improved properties relative to the unmodified protein. The combined length of URP sequences that are attached to a protein can be 40, 50, 60, 70, 80, 90, 100, 150, 200 or more amino acids.

[0138] The subject MURPs exhibit one or more improved properties as detailed below.

[0139] Improved Half-Life:

[0140] Adding a URP sequences to a pharmaceutically active protein can improve many properties of that protein. In particular, adding a long URP sequence can significantly increase the serum half-life of the protein. Such URPs typically contain amino acid sequences of at least about 40, 50, 60, 70, 80, 90, 100, 150, 200 or more amino acids.

[0141] The URPs can be fragmented such that the resulting protein contains multiple URPs, or multiple fragments of URPs. Some or all of these individual URP sequences may be shorter than 40 amino acids as long as the combined length of all URP sequences in the resulting protein is at least 30 amino acids. Preferably, the resulting protein has a combined length of URP sequences exceeding 40, 50, 60, 70, 80, 90, 100, 150, 200 or more amino acids. In one aspect, the fused URPs can increase the hydrodynamic radius of a protein and thus reduces its clearance from the blood by the kidney. The increase in the hydrodynamic radius of the resulting fusion

protein relative to the unmodified protein can be detected by ultracentrifugation, size exclusion chromatography, or light scattering.

[0142] Improved Tissue Selectivity:

[0143] Increasing the hydrodynamic radius can also lead to reduced penetration into tissues, which can be exploited to minimize side effects of a pharmaceutically active protein. It is well documented that hydrophilic polymers have a tendency to accumulate selectively in tumor tissue which is caused by the enhanced permeability and retention (EPR) effect. The underlying cause of the EPR effect is the leaky nature of tumor vasculature (McDonald, D. M., et al. (2002) *Cancer Res*, 62: 5381-5) and the lack of lymphatic drainage in tumor tissues. Therefore, the selectivity of pharmaceutically active proteins for tumor tissues can be enhanced by adding hydrophilic polymers. As such, the therapeutic index of a given pharmaceutically active protein can be increased via incorporating the subject URPS.

[0144] Protection from Degradation and Reduced Immunogenicity:

[0145] Adding URP sequences can significantly improve the protease resistance of a protein. URP sequences themselves can be designed to be protease resistant and by attaching them to a protein one can shield that protein from the access of degrading enzymes. URP sequences can be added to pharmaceutically active proteins with the goal of reducing undesirable interactions of the protein with other receptors or surfaces. To achieve this, it can be beneficial to add the URP sequences to the pharmaceutically active protein in proximity to the site of the protein that makes such undesirable contacts. In particular, one can add URP sequences to pharmaceutically active proteins with the goal of reducing their interactions with any component of the immune system to prevent an immune response against the product of the invention. Adding a URP sequence to a pharmaceutically active protein can reduce interaction with pre-existing antibodies or B-cell receptors. Furthermore, the addition of URP sequences can reduce the uptake and processing of the product of the invention by antigen presenting cells. Adding one or more URP sequence to a protein is a preferred way of reducing its immunogenicity as it will suppress an immune response in many species allowing one to predict the expected immunogenicity of a product in patients based on animal data. Such species independent testing of immunogenicity is not possible for approaches that are based on the identification and removal of human T cell epitopes or sequences comparison with human sequences.

[0146] Interruption of T Cell Epitopes:

[0147] URP sequences can be introduced into proteins in order to interrupt T cell epitopes. This is particularly useful for proteins that combine multiple separate functional modules. The formation of T cell epitopes requires that peptide fragments of a protein antigen bind to MHC. MHC molecules interact with a short segment of amino acids typically 9 contiguous residues of the presented peptides. The direct fusion of different binding modules in a protein molecule can lead to T cell epitopes that span two neighboring domains. By separating the functional modules by URP modules prevents the generation of such module-spanning T cell epitopes as illustrated in FIG. 7. The insertion of URP sequences between functional modules can also interfere with proteolytic processing in antigen presenting cells, which will lead to an additional reduction of immunogenicity. Another approach to reduce the risk of immunogenicity is to disrupt T cell epitopes

within functional modules of a product. In the case of microproteins, one approach is to have some of the intercysteine loops (those that are not involved in target binding) be glycine-rich. In microproteins, whose structure is due to a small number of cysteines, one could in fact replace most or all of the residues that are not involved in target binding with glycine, serine, glutamate, threonine, thus reducing the potential for immunogenicity while not affecting the affinity for the target. For instance, this can be carried out by performing a 'glycine-scan' of all residues, in which each residue is replaced by a glycine, then selecting the clones which retain target binding using phage display or screening, and then combining all of the glycine substitutions that are permitted. In general, functional modules have a much higher probability to contain T cell epitopes than URP modules. One can reduce the frequency of T cell epitopes in functional modules by replacing all or many non-critical amino acid residues with small hydrophilic residues like gly, ser, ala, glu, asp, asn, gln, thr. Positions in a functional module that allow replacement can be identified using a variety of random or structure based protein engineering approaches.

[0148] Improved Solubility:

[0149] Functional modules of a protein can have limited solubility. In particular, binding modules tend to carry hydrophobic residues on their surface, which can limit their solubility and can lead to aggregation. By spacing or flanking such functional modules with URP modules one can improve the overall solubility of the resulting product. This is in particular true for URP modules that carry a significant percentage of hydrophilic or charged residues. By separating functional modules with soluble URP modules one can reduce intramolecular interactions between these functional modules

[0150] Improved pH Profile and Homogeneity of Product Charge:

[0151] URP sequences can be designed to carry an excess of negative or positive charges. As a result they confer an electrostatic field to any fusion partner which can be utilized to shift the pH profile of an enzyme or a binding interaction. Furthermore, the electrostatic field of a charged URP sequence can increase the homogeneity of pKa values of surface charges of a protein product, which leads to sharpened pH profiles of ligand interactions and to sharpened separations by isoelectric focusing or chromatofocusing.

[0152] Improved Purification Properties Due to Sharper Product pKa:

[0153] Each amino acid in solution by itself has a single, fixed pKa, which is the pH at which its functional groups are half protonated. In a typical protein you have many types of residues and due to proximity and protein breathing effects, they also change each other's effective pKa in variable ways. Because of this, at a wide range of pH conditions, typical proteins can adopt hundreds of differently ionized species, each with a different molecular weight and net charge, due to large numbers of combinations of charged and neutral amino acid residues. This is referred to as a broad ionization spectrum and makes the analysis (ie Mass Spec) and purification of such proteins more difficult.

[0154] PEG is uncharged and does not affect the ionization spectrum of the protein it is attached to, leaving it with a broad ionization spectrum. However, a URP with a high content of Gly and Glu in principle exist in only two states: neutral (—COOH) when the pH is below the pKa of Glutamate and negatively charged (—COO^-) when the pH is above the pKa

of Glutamate. URP modules can form a single, homogeneously ionized type of molecule and can yield a single mass in mass spectrometry.

[0155] Where desired, MURPs can be expressed as a fusion with an URP having a single type of charge (Glu) distributed at constant spacing through the URP module. One may choose to incorporate 25-50 Glu residues per 20 kD of URP and all of these 25-50 residues would have very similar pKa.

[0156] In addition, adding 25-50 negative charges to a small protein like IFN, hGH or GCSF (with only 20 charged residues) will increase the charge homogeneity of the product and sharpen its isoelectric point, which will be very close to the pKa of free glutamate.

[0157] The increase in the homogeneity of the charge of the protein population has favorable processing properties, such as in ion exchange, isoelectric focusing, mass spec, etc. compared to traditional PEGylation.

[0158] Improved Formulation and/or Delivery:

[0159] Addition of URP sequences to pharmaceutically active proteins can significantly simplify the formulation and or the delivery of the resulting products. URP sequences can be designed to be very hydrophilic and as a result they improve the solubility of (for example) human proteins, which often contain hydrophobic patches that they use to bind to other human proteins. The formulation of such human proteins, like antibodies, can be quite challenging and often limits their concentration and delivery options. URPs can reduce product precipitation and aggregation and it allows one to use simpler formulations containing fewer ingredients, that are typically needed to stabilize a product in solution. The improved solubility of URP sequences-containing products allows to formulate these products at higher concentration and as a result one can reduce the injection volume for injectable products, which may enable home injection, which is limited to a very low injected volume. Addition of a URP sequence can also simplify the storage of the resulting formulated products. URP sequences can be added to pharmaceutically active proteins to facilitate their oral, pulmonary, rectal, or intranasal uptake. URP sequences can facilitate various modes of delivery because they allow higher product concentrations and improved product stability. Additional improvements can be achieved by designing URP sequences that facilitate membrane penetration.

[0160] Improved Production:

[0161] Adding URP sequences can have significant benefits for the production of the resulting product. Many recombinant products, especially native human proteins, have a tendency to form aggregates during production that can be difficult or impossible to dissolve and even when removed from the final product they may re-occur. These are usually due to hydrophobic patches by which these (native human) proteins contacted other (native human) proteins and mutating these residues is considered risky because of immunogenicity. However, URPs can increase the hydrophilicity of such proteins and enable their formulation without mutating the sequence of the human protein. URP sequences can facilitate the folding of a protein to reach its native state. Many pharmaceutically active proteins are produced by recombinant methods in a non-native aggregated state. These products need to be denatured and subsequently they are incubated under conditions that allow the proteins to fold into their native active state. A frequent side reaction during renaturation is the formation of aggregates. The fusion of URP sequences to a protein significantly reduces its tendency to

form aggregates and thus it facilitates the folding of the pharmaceutically active component of the product. URP-containing products are much easier to prepare as compared to polymer-modified proteins. Chemical polymer-modification requires extra modification and purification steps after the active protein has been purified. In contrast, URP sequences can be manufactured using recombinant DNA methods together with the pharmaceutically active protein. The products of the invention are also significantly easier to characterize compared to polymer-modified products. Due to the recombinant production process one can obtain more homogeneous products with defined molecular characteristics. URP sequences can also facilitate the purification of a product. For instance URP sequences can include subsequences that can be captured by affinity chromatography. An example are sequences rich in histidine, which can be captured on resins with immobilized metals like nickel. URP sequences can also be designed to have an excess of negatively or positively charged amino acids. As a result they can significantly impact the net charge of a product, which can facilitate product purification by ion-exchange chromatography or preparative electrophoresis.

[0162] The subject MURPs can contain a variety of modules, including but not limited to binding modules, effector modules, multimerization modules, C-terminal modules, and N-terminal modules. FIG. 1 depicts an exemplary MURP having multiple modules. However, MURPs can also have relatively simple architectures that are illustrated in FIG. 2. MURPs can also contain fragmentation sites. These can be protease-sensitive sequences or chemically sensitive sequences that can be preferentially cleaved when the MURPs reach their target site.

[0163] Binding Module (BM):

[0164] The MURPs of the present invention may comprise one or more binding modules. Binding module (BM) refers to a peptide or protein sequence that can bind specifically to one or several targets, which may be one or more therapeutic targets or accessory targets, such as for cell-, tissue- or organ targeting. BMs can be linear or cyclic peptides, cysteine-constrained peptides, microproteins, scaffold proteins (e.g., fibronectin, ankyrins, crystalline, streptavidin, antibody fragments, domain antibodies), peptidic hormones, growth factors, cytokines, or any type of protein domain, human or non-human, natural or non-natural, and they may be based on a natural scaffold or not based on a natural scaffold, or based on combinations or they may be fragments of any of the above. Optionally, these BMs can be engineered by adding, removing or replacing one or multiple amino acids in order to enhance their binding properties, their stability, or other properties. Binding modules can be obtained from natural proteins, by design or by genetic package display, including phage display, cellular display, ribosomal display or other display methods. Binding modules may bind to the same copy of the same target, which results in avidity, or they may bind to different copies of the same target (which can result in avidity if these copies are somehow connected or linked, such as by a cell membrane), or they may bind to two unrelated targets (which yields avidity if these targets are somehow linked, such as by a membrane). Binding modules can be identified by screening or otherwise analyzing random libraries of peptides or proteins.

[0165] Particularly desirable binding modules are those that upon incorporation into a MURP, the MURP yield a desirable Tepitope score. The Tepitope score of a protein is

the log of the Kd (dissociation constant, affinity, off-rate) of the binding of that protein to multiple of the most common human MHC alleles, as disclosed in Sturniolo, T. et al. (1999) Nature Biotechnology 17:555). The score ranges over at least 15 logs, from about 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0, -1, -2, -3, -4, -5 ($10e^{10}$ Kd) to about -5. Preferred MURPs yield a score less than about -3.5 [KKW: On absolute scale?]

[0166] Of particular interest are also binding modules comprising disulfide bonds formed by pairing two cysteine residues. In certain embodiments, the binding modules comprise polypeptides having high cysteine content or high disulfide density (HDD). Binding modules of the HDD family typically have 5-50% (5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45 or 50%) cysteine residues and each domain typically contains at least two disulfides and optionally a co-factor such as calcium or another ion.

[0167] The presence of HDD scaffold allows these modules to be small but still adopt a relatively rigid structure. Rigidity is important to obtain high binding affinities, resistance to proteases and heat, including the proteases involved in antigen processing, and thus contributes to the low or non-immunogenicity of these modules. The disulfide framework folds the modules without the need for a large number of hydrophobic side chain interactions in the interior of most modules. The small size is also advantageous for fast tissue penetration and for alternative delivery such as oral, nasal, intestinal, pulmonary, blood-brain-barrier, etc. In addition, the small size also helps to reduce immunogenicity. A higher disulfide density is obtainable, either by increasing the number of disulfides or by using domains with the same number of disulfides but fewer amino acids. It is also desirable to decrease the number of non-cysteine fixed residues, so that a higher percentage of amino acids is available for target binding.

[0168] The cysteine-containing binding modules can adopt a wide range of disulfide bonding patterns (DBPs). For example, two-disulfide modules can have three different disulfide bonding patterns (DBPs), three-disulfide modules can have 15 different DBPs and four-disulfide modules have up to 105 different DBPs. Natural examples exist for all of the 2SS DBPs, the majority of the 3SS DBPs and less than half of the 4SS DBPs. In one aspect, the total number of disulfide bonding patterns can be calculated according to the formula:

$$\prod_{i=1}^n 2i - 1,$$

wherein n=the predicted number of disulfide bonds formed by the cysteine residues, and wherein Π represents the product of (2i-1), where i is a positive integer ranging from 1 up to n.

[0169] Accordingly, in one embodiment, the modules used in MURPs are natural or non-naturally occurring cysteine (C)-containing scaffold exhibiting a binding specificity towards a target molecule, wherein the non-naturally occurring cysteine (C)-containing scaffold comprise intra-scaffold cysteines according to a pattern selected from the group of permutations represented by the formula

$$\prod_{i=1}^n 2i - 1,$$

wherein n equals to the predicted number of disulfide bonds formed by the cysteine residues, and wherein Π represents the product of (2i-1), where i is a positive integer ranging from 1 up to n. In one aspect, the natural or non-naturally occurring cysteine (C)-containing module comprises a polypeptide having two disulfide bonds formed by pairing cysteines contained in the polypeptide according to a pattern selected from the group consisting of C^{1-2, 3-4}, C^{1-3, 2-4}, and C^{1-4, 2-3}, wherein the two numerical numbers linked by a hyphen indicate which two cysteines counting from N-terminus of the polypeptide are paired to form a disulfide bond. In another aspect, the natural or non-naturally occurring cysteine (C)-containing module comprises a polypeptide having three disulfide bonds formed by pairing intra-scaffold cysteines according to a pattern selected from the group consisting of C^{1-2, 3-4, 5-6}, C^{1-2, 3-5, 4-6}, C^{1-2, 3-6, 4-5}, C^{1-3, 2-4, 5-6}, C^{1-3, 2-5, 4-6}, C^{1-3, 2-6, 4-5}, C^{1-4, 2-3, 5-6}, C^{1-4, 2-6, 3-5}, C^{1-5, 2-3, 4-6}, C^{1-5, 2-4, 3-6}, C^{1-5, 2-6, 3-4}, C^{1-6, 2-3, 4-5}, and C^{1-6, 2-5, 3-4}, wherein the two numerical numbers linked by a hyphen indicate which two cysteines counting from N-terminus of the polypeptide are paired to form a disulfide bond. In yet another aspect, the natural or non-naturally occurring cysteine (C)-containing module comprises a polypeptide having at least four disulfide bonds formed by pairing cysteines contained in the polypeptide according to a pattern selected from the group of permutations defined by the formula above. In yet another aspect, the natural or non-naturally occurring cysteine (C)-containing module comprises a polypeptide having at least five, six, or more disulfide bonds formed by pairing intra-protein cysteines according to a pattern selected from the group of permutations represented by the formula above. Any of the cysteine-containing proteins or scaffolds disclosed in the co-pending application Ser. Nos. 11/528,927 and 11/528,950, which are incorporated herein by reference in their entirety] are candidate binding modules.

[0170] Binding modules can also be selected from libraries of cysteine-constrained cyclic peptides with 4, 5, 6, 7, 8, 9, 10, 11 and 12 randomized or partially randomized amino acids between the disulfide-bonded cysteines (e.g., in a build-up manner), and in some cases additional randomized amino acids on the outside of the cystine pair can be constructed using a variety of methods. Library members with specificity for a target of interest can be identified using various methods including phage display, ribosomal display, yeast display and other methods known in the art. Such cyclic peptides can be utilized as binding modules in MURPs. In a preferred embodiment one can further engineer cysteine-constrained peptides to increase their binding affinity, proteolytic stability, and/or specificity using buildup approaches that lead to binding modules containing more than one disulfide bond. One particular buildup approach is illustrated in FIG. 25. It is based on the addition of a single cysteine plus multiple randomized residues on the N-terminal side of the previously selected cyclic peptide, as well as on the C-terminal side. One can generate libraries that have been designed as illustrated in FIG. 25. Binding modules with improved properties can be identified by phage display or similar methods. Such buildup libraries can contain between 1 and 12 random positions on

the N-terminal as well as on the C-terminal side of a cyclic peptide. The distance between the cysteine residues in the newly added random flanks and the cysteine residues in the cyclic peptide can be varied between 1 and 12 residues. Such libraries will contain four cysteine residues per library member, with two cysteines resulting from the original cyclic peptide and two cysteine residues in the newly added flanks. This approach favors a 1-4 2-3 DBP or a change in DBP, breaking up the preexisting 1-2 disulfide (=2-3 in the 4-cysteine construct) to form a 1-2 3-4 or a 1-3 2-4 DBP. Such buildup approaches can be performed with clone-specific primers so that it leaves no fixed sequence between the library areas as shown in FIG. 25, or it can be performed with primers that use (and thus leave) a fixed sequence on both sides of the previously selected peptide and therefore these same primers can be used for any previously selected clone as illustrated in FIG. 26. The method illustrated in FIG. 26 can be applied to a collection of cyclic peptides with specificity for a target of interest. Both buildup approaches were shown to work for anti-VEGF affinity maturation by build-up. This approach can be repeated to generate binding modules with six or more cysteine residues.

[0171] Another buildup of a one-disulfide into a 2-disulfide sequence is illustrated in FIG. 27. It involves the dimerization of a previously selected pool of 1-disulfide peptides with itself so that the preselected peptide pool ends up in the N-terminal as well as in the C-terminal position. This approach favors the build up of 2-disulfide sequences that recognize two separate epitopes on a target.

[0172] Another buildup approach involves the addition of a (partially) randomized sequence of 6-15 residues containing two cysteines that are spaced 4, 5, 6, 7, 8, 9, or 10 amino acids apart, with optionally additional randomized positions outside the linked cysteines. This 2-cysteine random sequence is added on the N-terminal side of the previously selected peptide, or on the C-terminal side. This approach favors a 1-2 3-4 DBP, although other DBPs may be formed. This approach can be repeated to generate binding modules with six or more cysteine residues.

[0173] Binding modules can be constructed based on natural protein scaffolds. Such scaffolds can be identified by data base searching. Libraries that are based on natural scaffolds can be subjected to phage display panning followed by screening to identify sequences that specifically bind to a target of interest.

[0174] A wide selection of natural scaffolds is available for constructing the binding modules. The choice of a particular scaffold will depend on the intended target. Non-limiting examples of natural scaffolds include snake-toxin-like proteins such as snake venom toxins and extracellular domain of human cell surface receptors. Non-limiting examples of snake venom toxins are Erabutoxin B, gamma-Cardiotoxin, Fasiculin, Muscarinic toxin, Erabutoxin A, Neurotoxin I, Cardiotoxin V4II (Toxin III), Cardiotoxin V, alpha-Cobrotoxin, long Neurotoxin I, FS2 toxin, Bungarotoxin, Bucandin, Cardiotoxin CTXI, Cardiotoxin CTX IIB, Cardiotoxin II, Cardiotoxin III, Cardiotoxin IV, Cobrotoxin 2, alpha-toxins, Neurotoxin II (cobrotoxin B), Toxin B (long neurotoxin), Candotoxin, Bucain. Non-limiting examples of extracellular domain of (human) cell surface receptors include CD59, Type II activin receptor, BMP receptor Ia ectodomain, TGF-beta type II receptor extracellular domain. Other natural scaffolds include but are not limited to A-domains, EGF, Ca-EGF, TNF-R, Notch, DSL, Trefoil, PD, TSP1, TSP2, TSP3, Anato,

Integrin Beta, Thyroglobulin, Defensin 1, Defensin 2, Cyclotide, SHKT, Disintegrins, Myotoxins, Gamma-Thionins, Conotoxin, Mu-Conotoxin, Omega-Atracotoxins, Delta-Atracotoxins, as well as additional families disclosed in co-pending application Ser. Nos. 11/528,927 and 11/528,950, which are incorporated herein in their entirety.

[0175] A large variety of methods has been described that allow one to identify binding molecules in a large library of variants. One method is chemical synthesis. Library members can be synthesized on beads such that each bead carries a different peptide sequence. Beads that carry ligands with a desirable specificity can be identified using labeled binding partners. Another approach is the generation of sub-libraries of peptides which allows one to identify specific binding sequences in an iterative procedure (Pinilla, C., et al. (1992) *BioTechniques*, 13: 901-905). More commonly used are display methods where a library of variants is expressed on the surface of a phage, protein, or cell. These methods have in common, that that DNA or RNA coding for each variant in the library is physically linked to the ligand. This enables one to detect or retrieve the ligand of interest and then determine its peptide sequence by sequencing the attached DNA or RNA. Display methods allow one skilled in the art to enrich library members with desirable binding properties from large libraries of random variants. Frequently, variants with desirable binding properties can be identified from enriched libraries by screening individual isolates from an enriched library for desirable properties. Examples of display methods are fusion to lac repressor (Cull, M., et al. (1992) *Proc. Natl. Acad. Sci. USA*, 89: 1865-1869), cell surface display (Wittrup, K. D. (2001) *Curr Opin Biotechnol*, 12: 395-9). Of particular interest are methods where random peptides or proteins are linked to phage particles. Commonly used are M13 phage (Smith, G. P., et al. (1997) *Chem Rev*, 97: 391-410) and T7 phage (Danner, S., et al. (2001) *Proc Natl Acad Sci USA*, 98: 12954-9). There are multiple methods available to display peptides or proteins on M13 phage. In many cases, the library sequence is fused to the N-terminus of peptide pIII of the M13 phage. Phage typically carry 3-5 copies of this protein and thus phage in such a library will in most cases carry between 3-5 copies of a library member. This approach is referred to as multivalent display. An alternative is phagemid display where the library is encoded on a phagemid. Phage particles can be formed by infection of cells carrying a phagemid with a helper phage. (Lowman, H. B., et al. (1991) *Biochemistry*, 30: 10832-10838). This process typically leads to monovalent display. In some cases, monovalent display is preferred to obtain high affinity binders. In other cases multivalent display is preferred (O'Connell, D., et al. (2002) *J Mol Biol*, 321: 49-56).

[0176] A variety of methods have been described to enrich sequences with desirable characteristics by phage display. One can immobilize a target of interest by binding to immunotubes, microtiter plates, magnetic beads, or other surfaces. Subsequently, a phage library is contacted with the immobilized target, phage that lack a binding ligand are washed away, and phage carrying a target specific ligand can be eluted by a variety of conditions. Elution can be performed by low pH, high pH, urea or other conditions that tend to break protein-protein contacts. Bound phage can also be eluted by adding *E. coli* cells such that eluting phage can directly infect the added *E. coli* host. An interesting protocol is the elution with protease which can degrade the phage-bound ligand or the immobilized target. Proteases can also be utilized as tools to enrich

protease resistant phage-bound ligands. For instance, one can incubate a library of phage-bound ligands with one or more (human or mouse) proteases prior to panning on the target of interest. This process degrades and removes protease-labile ligands from the library (Kristensen, P., et al. (1998) *Fold Des*, 3: 321-8). Phage display libraries of ligands can also be enriched for binding to complex biological samples. Examples are the panning on immobilized cell membrane fractions (Tur, M. K., et al. (2003) *Int J Mol Med*, 11: 523-7), or entire cells (Rasmussen, U. B., et al. (2002) *Cancer Gene Ther*, 9: 606-12; Kelly, K. A., et al. (2003) *Neoplasia*, 5: 437-44). In some cases one has to optimize the panning conditions to improve the enrichment of cell specific binders from phage libraries (Watters, J. M., et al. (1997) *Immunotechnology*, 3: 21-9). Phage panning can also be performed in live patients or animals. This approach is of particular interest for the identification of ligands that bind to vascular targets (Arap, W., et al. (2002) *Nat Med*, 8: 121-7).

[0177] A variety of cloning methods are available that allow one skilled in the art to generate libraries of DNA sequences that encode libraries of peptides. Random mixtures of nucleotides can be utilized to synthesize oligonucleotides that contain one or multiple random positions. This process allows one to control the number of random positions as well as the degree of randomization. In addition, one can obtain random or semi-random DNA sequences by partial digestion of DNA from biological samples. Random oligonucleotides can be used to construct libraries of plasmids or phage that are randomized in pre-defined locations. This can be done by PCR fusion as described in (de Kruif, J., et al. (1995) *J Mol Biol*, 248: 97-105). Other protocols are based on DNA ligation (Felici, F., et al. (1991) *J Mol Biol*, 222: 301-10; Kay, B. K., et al. (1993) *Gene*, 128: 59-65). Another commonly used approach is Kunkel mutagenesis where a mutagenized strand of a plasmid or phagemid is synthesized using single stranded cyclic DNA as template. See, Sidhu, S. S., et al. (2000) *Methods Enzymol*, 328: 333-63; Kunkel, T. A., et al. (1987) *Methods Enzymol*, 154: 367-82.

[0178] Kunkel mutagenesis uses templates containing randomly incorporated uracil bases which can be obtained from *E. coli* strains like CJ236. The uracil-containing template strand is preferentially degraded upon transformation into *E. coli* while the in vitro synthesized mutagenized strand is retained. As a result most transformed cells carry the mutagenized version of the phagemid or phage. A valuable approach to increase diversity in a library is to combine multiple sub-libraries. These sub-libraries can be generated by any of the methods described above and they can be based on the same or on different scaffolds.

[0179] A useful method to generate large phage libraries of short peptides has been recently described (Scholle, M. D., et al. (2005) *Comb Chem High Throughput Screen*, 8: 545-51). This method is related to the Kunkel approach but it does not require the generation of single stranded template DNA that contains random uracil bases. Instead, the method starts with a template phage that carries one or more mutations close to the area to be mutagenized and said mutation renders the phage non-infective. The method uses a mutagenic oligonucleotide that carries randomized codons in some positions and that correct the phage-inactivating mutation in the template. As a result, only mutagenized phage particles are infective after transformation and very few parent phage are contained in such libraries. This method can be further modified in several ways. For instance, one can utilize multiple

mutagenic oligonucleotides to simultaneously mutagenize multiple discontinuous regions of a phage. We have taken this approach one step further by applying it to whole microproteins of >25, 30, 35, 40, 45, 50, 55 and 60 amino acids, instead of short peptides of <10, 15 or 20 amino acids, which poses an additional challenge. This approach now yields libraries of more than 10e10 transformants (up to 10e11) with a single transformation, so that a single library with a diversity of 10e12 is expected from 10 transformations.

[0180] Another variation of the Scholle method is to design the mutagenic oligonucleotide such that an amber stop codon in the template is converted into an ochre stop codon, and an ochre into an amber in the next cycle of mutagenesis. In this case the template phage and the mutagenized library members must be cultured in different suppressor strains of *E. coli*, alternating an ochre suppressor with amber suppressor strains. This allows one to perform successive rounds of mutagenesis of a phage by alternating between these two types of stop codons and two suppressor strains.

[0181] Yet another variation of the Scholle approach involves the use of megaprimers with a single stranded phage DNA template. The megaprimer is a long ssDNA that was generated from the library inserts of the selected pool of phage from the previous round of panning. The goal is to capture the full diversity of library inserts from the previous pool, which was mutagenized in one or more areas, and transfer it to a new library in such a way that an additional area can be mutagenized. The megaprimer process can be repeated for multiple cycles using the same template which contains a stop-codon in the gene of interest. The megaprimer is a ssDNA (optionally generated by PCR) which contains 1) 5' and 3' overlap areas of at least 15 bases for complementarity to the ssDNA template, and 2) one or more previously selected library areas (1, 2, 3, 4 or more) which were copied (optionally by PCR) from the pool of previously selected clones, and 3) a newly mutagenized library area that is to be selected in the next round of panning. The megaprimer is optionally prepared by 1) synthesizing one or more oligonucleotides encoding the newly synthesized library area and 2) by fusing this, optionally using overlap PCR, to a DNA fragment (optionally obtained by PCR) which contains any other library areas which were previously optimized. Run-off or single stranded PCR of the combined (overlap) PCR product is used to generate the single stranded megaprimer that contains all of the previously optimized areas as well as the new library for an additional area that is to be optimized in the next panning experiment. This approach is expected to allow affinity maturation of proteins using multiple rapid cycles of library creation generating 10e11 to 10e12 diversity per cycle, each followed by panning.

[0182] A variety of methods can be applied to introduce sequence diversity into (previously selected or naïve) libraries of microproteins or to mutate individual microprotein clones with the goal of enhancing their binding or other properties like manufacturing, stability or immunogenicity. In principle, all the methods that can be used to generate libraries can also be used to introduce diversity into enriched (previously selected) libraries of microproteins. In particular, one can synthesize variants with desirable binding or other properties and design partially randomized oligonucleotides based on these sequences. This process allows one to control the positions and degree of randomization. One can deduce the utility of individual mutations in a protein from sequence data of multiple variants using a variety of computer algo-

rithms (Jonsson, J., et al. (1993) *Nucleic Acids Res.* 21: 733-9; Amin, N., et al. (2004) *Protein Eng Des Sel.* 17: 787-93). Of particular interest for the re-mutagenesis of enriched libraries is DNA shuffling (Stemmer, W. P. C. (1994) *Nature*, 370: 389-391), which generates recombinants of individual sequences in an enriched library. Shuffling can be performed using a variety modified PCR conditions and templates may be partially degraded to enhance recombination. An alternative is the recombination at pre-defined positions using restriction enzyme-based cloning. Of particular interest are methods utilizing type IIS restriction enzymes that cleave DNA outside of their sequence recognition site (Collins, J., et al. (2001) *J Biotechnol.* 74: 317-38. Restriction enzymes that generate non-palindromic overhangs can be utilized to cleave plasmids or other DNA encoding variant mixtures in multiple locations and complete plasmids can be re-assembled by ligation (Berger, S. L., et al. (1993) *Anal Biochem.* 214: 571-9). Another method to introduce diversity is PCR-mutagenesis where DNA sequences encoding library members are subjected to PCR under mutagenic conditions. PCR conditions have been described that lead to mutations at relatively high mutation frequencies (Leung, D., et al. (1989) *Technique*, 1: 11-15). In addition, a polymerase with reduced fidelity can be employed (Vanhercke, T., et al. (2005) *Anal Biochem.* 339: 9-14). A method of particular interest is based on mutator strains (Irving, R. A., et al. (1996) *Immunotechnology*, 2: 127-43; Coia, G., et al. (1997) *Gene*, 201: 203-9). These are strains that carry defects in one or more DNA repair genes. Plasmids or phage or other DNA in these strains accumulate mutations during normal replication. One can propagate individual clones or enriched populations in mutator strains to introduce genetic diversity. Many of the methods described above can be utilized in an iterative process. One can apply multiple rounds of mutagenesis and screening or panning to entire genes, or to portions of a gene, or one can mutagenize different portions of a protein during each subsequent round (Yang, W. P., et al. (1995) *J Mol Biol.* 254: 392-403).

[0183] The libraries can be further treated to reduce artifacts. Known artifacts of phage panning include 1) non-specific binding based on hydrophobicity, and 2) multivalent binding to the target, either due to a) the pentavalency of the pIII phage protein, or b) due to the formation of disulfides between different microproteins, resulting in multimers, or c) due to high density coating of the target on a solid support and 3) context-dependent target binding, in which the context of the target or the context of the microproteins becomes critical to the binding or inhibition activity. Different treatment steps can be taken to minimize the magnitude of these problems. For example, such treatments are applied to the whole library, but some useful treatments that remove bad clones can only be applied to pools of soluble proteins or only to individual soluble proteins.

[0184] Libraries of cysteine-containing scaffolds are likely to contain free thiols, which can complicate directed evolution by cross-linking to other proteins. One approach is to remove the worst clones from the library by passing it over a free-thiol column, thus removing all clones that have one or more free sulfhydryls. Clones with free SH groups can also be reacted with biotin-SH reagents, enabling efficient removal of clones with reactive SH groups using Streptavidin columns. Another approach is to not remove the free thiols, but to inactivate them by capping them with sulfhydryl-reactive chemicals such as iodoacetic acid. Of particular interest are

bulky or hydrophilic sulfhydryl reagents that reduce the non-specific target binding or modified variants.

[0185] Examples of context dependence are all of the constant sequences, including pIII protein, linkers, peptide tags, biotin-streptavidin, Fc and other fusion proteins that contribute to the interaction. The typical approach for avoiding context-dependence involves switching the context as frequently as practical in order to avoid buildup. This may involve alternating between different display systems (ie M13 versus T7, or M13 versus Yeast), alternating the tags and linkers that are used, alternating the (solid) support used for immobilization (ie immobilization chemistry) and alternating the target proteins itself (different vendors, different fusion versions).

[0186] Library treatments can also be used to select for proteins with preferred qualities. One option is the treatment of libraries with proteases in order to remove unstable variants from the library. The proteases used are typically those that would be encountered in the application. For pulmonary delivery, one would use lung proteases, for example obtained by a pulmonary lavage. Similarly, one would obtain mixtures of proteases from serum, saliva, stomach, intestine, skin, nose, etc. However, it is also possible to use mixtures of single purified proteases. An extensive list of proteases is shown in [Appendix E]. The phage themselves are exceptionally resistant to most proteases and other harsh treatments.

[0187] For example, it is possible to select the library for the most stable structures, ie those with the strongest disulfide bonds, by exposing it to increasing concentrations of reducing agents (ie DTT or betamercaptoethanol), thus eliminating the least stable structures first. One would typically use reducing agent (ie DTT, BME, other) concentrations from 2.5 mM, to 5 mM, 10 mM, 20 mM, 30 mM, 40 mM, 50 mM, 60 mM, 70 mM, 80 mM, 90 mM or even 100 mM, depending on the desired stability.

[0188] It is also possible to select for clones that can be efficiently refolded in vitro, by reducing the entire display library with a high level of reducing agent, followed by gradually re-oxidizing the protein library to reform the disulfides, followed by the removal of clones with free SH groups, as described above. This process can be applied once or multiple times to eliminate clones that have low refolding efficiency in vitro.

[0189] One approach is to apply a genetic selection for protein expression level, folding and solubility as described by A. C. Fisher et al. (2006) Genetic selection for protein solubility enabled by the folding quality control feature of the twin-arginine translocation pathway. Protein Science (online). After panning of display libraries (optional), one would like to avoid screening thousands of clones at the protein level for target binding, expression level and folding. An alternative is to clone the whole pool of selected inserts into a betalactamase fusion vector, which, when plated on betalactam, the authors demonstrated to be selective for well-expressed, fully disulfide bonded and soluble proteins.

[0190] Following M13 Phage display of protein libraries and panning on targets for one or more cycles, there are a variety of ways to proceed, including (1) screening of individual phage clones by phage ELISA, which measures the number of phage particles (using anti-M13 antibodies) that bind to an immobilized target; (2) transferring from M13 into T7 phage display libraries. The second approach is particularly useful in reducing the occurrence of false positives based on valency. Any single library format tends to favor clones that can form high-avidity contacts with the target.

This is the reason that screening of soluble proteins is important, although this is a tedious solution. The multivalency achieved in T7 phage display is likely very different from that achieved in M13 display, and cycling between T7 and M13 can be an excellent approach to reducing the occurrence of false positives based on valency.

[0191] Filter lift is another methodology that can be with bacterial colonies grown at high density on large agar plates (10e2-10e5). Small amounts of some proteins are secreted into the media and end up bound to the filter membrane (nitrocellulose or nylon). The filters are then blocked in non-fat milk, 1% Casein hydrolysate or a 1% BSA solution and incubated with the target protein that has been labeled with a fluorescent dye or an indicator enzyme (directly or indirectly via antibodies or via biotin-streptavidin). The location of the colony is determined by overlaying the filter on the back of the plate and all of the positive colonies are selected and used for additional characterization. The advantage of filter lifts is that it can be made to be affinity-selective by reading the signal after washing for different periods of time. The signal of high affinity clones 'fades' slowly, whereas the signal of low affinity clones fades rapidly. Such affinity characterization typically requires a 3-point assay with a well-based assay and may provide better clone-to-clone comparability than well-based assays. Gridding of colonies into an array is useful since it minimizes differences due to colony size or location.

[0192] N-Terminal Modules:

[0193] The subject MURPs can contain N-terminal modules (NM), which are particularly useful e.g., in facilitating production of the MURPs. The NM can be a single methionine residue when the products is expressed in the *E. coli* cytoplasm. A typical product format is an URP fused to a therapeutic protein, which is expressed in the bacterial cytoplasm so that the N-terminus is formyl-methionine. The formyl-methionine can either be permanent or temporary, if it is removed by biological or chemical processing.

[0194] The NM can also be a peptide sequence that has been engineered for proteolytic processing, which can be used to remove tags or to remove fusion proteins. The N-terminal module can be engineered to facilitate the purification of the MURP by including an affinity tag such as the Flag-, Myc-, HA- or His-tag. The N-terminal module can also include an affinity tag that can be used for the detection of the MURP. An NM can be engineered or selected for high-level expression of the MURP. It can also be engineered or selected to enhance the protease resistance of the resulting MURP. MURPs can be produced with an N-terminal module that facilitates expression and/or purification. This N-terminal module can be cleaved off during the production process with a protease, such that the final product does not contain an N-terminal module.

[0195] By optimizing the amino acid and codon choice of the N-terminal module one can increase recombinant production. The N-terminal module can also contain a processing site that can be cleaved by a specific protease like factor Xa, thrombin, or enterokinase, Tomato Etch Virus (TEV) protease. Processing sites can also be designed to be cleavable by chemical hydrolysis. An example is the amino acid sequence asp-pro that can be cleaved under acidic conditions. An N-terminal module can also be designed to facilitate the purification of a MURP. For example, N-terminal modules can be designed to contain multiple his residues which allow product capture by immobilized metal chromatography. N-terminal

modules can contain peptide sequences that can be specifically captured or detected by antibodies. Examples are FLAG, HA, c-myc.

[0196] C-Terminal Modules:

[0197] MURPs can contain a C-terminal module, which are particularly useful e.g., in facilitating production of the MURPs. For example, C-terminal module can comprise a cleavage site to effect proteolytic processing to remove sequences that are fused and hence increasing protein expression or facilitating purification. In particular, the C-terminal module can also contain a processing site that can be cleaved by a specific protease like factor Xa, thrombin, TEV protease or enterokinase. Processing sites can also be designed to be cleavable by chemical hydrolysis. An example is the amino acid sequence asp-pro that can be cleaved under acidic conditions. The C-terminal module can be an affinity tag aimed at facilitating the purification of the MURP. For example, C-terminal modules can be designed to contain multiple his residues which allow product capture by immobilized metal chromatography. C-terminal modules can contain peptide sequences that can be specifically captured or detected by antibodies. Non-limiting examples of the tags include FLAG-, HA-, c-myc, or His-tag. C-terminal module can also be engineered or selected to enhance the protease resistance of the resulting MURP.

[0198] Where desired, the N-terminus of the protein can be linked to its own C-terminus. For example, linking these two modules can be carried out by creating an amino acid-like natural linkage (peptide bond) or by using an exogenous linking entity. Of particular interest are cyclotides, a family of small proteins in which this occurs naturally. Adopting a structural format like cyclotides is expected to provide additional stability against exo-proteases. Such intramolecular linkage typically works better at lower protein concentrations.

[0199] Effector Modules:

[0200] MURPs can comprise one or multiple effector modules (EMs), or none at all. Effector modules typically do not provide the targeting, but they provide an activity required for therapeutic effect, like cell-killing. EMs can be pharmaceutically active small molecules (ie toxic drugs), peptides or proteins. Non-limiting examples are cytokines, antibodies enzymes, growth factors, hormones, receptors, receptor agonists or antagonists, whether whole or a fragment or domain thereof. Effector modules can also comprise peptide sequences that carry chemically linked small molecule drugs, whether synthetic or natural. Optionally, these effector molecules can be linked to the effector module via chemical linkers, which may or may not be cleaved under selected conditions leading to a release of the toxic activity. EMs can also include radioisotopes and their chelates, as well as various labels for PET and MRI. Effector modules can also be toxic to a cell or a tissue. Of particular interest are MURPs that contain toxic effector modules and binding modules with specificity for a diseased tissue or disease cell type. Such MURPs can specifically accumulate in a diseased tissue or in diseased cells and the can exert their toxic action preferentially in the diseased cells or tissues. Listed below are exemplary effector modules.

[0201] Enzymes—Effector modules can be enzymes. Of particular interest are enzymes that degrade metabolites that are critical for cellular growth like carbohydrates or amino acids or lipids or co-factors. Other examples for effector modules with enzymatic activity are RNase, DNase, and

phosphatase, asparaginase, histidinase, arginase, betalactamase. Effector modules with enzymatic activity can be toxic when delivered to a tissue or cell. Of particular interest are MURPs that combine effector modules that are toxic and binding modules that bind specifically to a diseased tissue. Enzymes that convert an inactive prodrug into an active drug at the tumor site are also potential effector modules.

[0202] Drug—The subject MURP can contain an effector that is a drug. Where desired, sequences can be designed for the organ-selective delivery of drug molecules. An example is illustrated in FIG. 8. An URP sequence can be fused to a protein that preferentially binds to diseased tissue. The same URP sequence can contain one or more amino acid residues that can be modified for the attachment of drug molecules. Such a conjugate can bind to diseased tissue with high specificity and the attached drug molecules can result in local action while minimizing systemic drug exposure. The MURP can be designed to facilitate the release of drug molecules at the target site by introducing protease-sensitive sites that can be cleaved by native proteases at the site of desired action. A significant advantage of using URP sequences for the design of drug delivery constructs is that one can avoid undesirable interactions between the drug molecule and the targeting domain of the construct. Many drug molecules that can be conjugated to targeting domains have significant hydrophobicity and the resulting conjugates tend to aggregate. By adding hydrophilic URP sequences to such constructs one can improve the solubility of the resulting delivery constructs and as a consequence reduce the aggregation tendency. Furthermore, one can increase the number of drug molecules that can be fused to a targeting domain by adding long URP sequences. In addition, the use of URP sequences allows one to optimize the distance between the drug conjugation sites to facilitate complete conjugation. The list of suitable drugs includes but are not limited to chemotherapeutic agents such as thiotepa and cyclophosphamide (CYTOXANTM); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabacin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitioestanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide,

mitotane, trilostane; folic acid replenisher such as frolic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; duocarmycin, maytansin, auristatin, elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguanzone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.RTM; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOLTM, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERETTM, Rhone-Poulenc Rorer, Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-1); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, goserelin, doxorubicin, daunomycin, duocarmycin, vincristin, and vinblastin.

[0203] Other drugs that can be used as the effector modules include those that are useful for treating inflammatory conditions, cardiac diseases, infectious diseases, respiratory diseases, autoimmune diseases, neuronal and muscular disorders, metabolic disorders, and cancers.

[0204] Additional drugs that can be used as the effectors in MURPs include agents for pain and inflammation such as histamine and histamine antagonists, bradykinin and bradykinin antagonists, 5-hydroxytryptamine (serotonin), lipid substances that are generated by biotransformation of the products of the selective hydrolysis of membrane phospholipids, eicosanoids, prostaglandins, thromboxanes, leukotrienes, aspirin, nonsteroidal anti-inflammatory agents, analgesic-antipyretic agents, agents that inhibit the synthesis of prostaglandins and thromboxanes, selective inhibitors of the inducible cyclooxygenase, selective inhibitors of the inducible cyclooxygenase-2, autacoids, paracrine hormones, somatostatin, gastrin, cytokines that mediate interactions involved in humoral and cellular immune responses, lipid-derived autacoids, eicosanoids, β -adrenergic agonists, ipratropium, glucocorticoids, methylxanthines, sodium channel blockers, opioid receptor agonists, calcium channel blockers, membrane stabilizers and leukotriene inhibitors.

[0205] Other drugs that can be used as effector include agents for the treatment of peptic ulcers, agents for the treatment of gastroesophageal reflux disease, prokinetic agents, antiemetics, agents used in irritable bowel syndrome, agents used for diarrhea, agents used for constipation, agents used for inflammatory bowel disease, agents used for biliary disease, agents used for pancreatic disease.

[0206] Radionuclides—MURPs can be designed for the tissue-targeted delivery of radionuclides as well as for imaging with radionuclides. URPs are ideal for imaging because the half-life can be optimized by changing the length of the URP. For most imaging applications a moderately long URP is likely to be preferred, providing a half-life of 5 minutes to a few hours, not days or weeks. MURPs can be designed such that they only contain a single or a small defined number of amino groups that can be modified with chelating agents (such as DOTA) for radio isotopes such as technetium, indium, yttrium, (EXPAND). Alternative methods of conjugation are through reserved cysteine side chains. Such radionuclide-carrying MURPs can be employed for the treatment of tumors or other diseased tissues, as well as for imaging.

[0207] Many pharmaceutically active proteins or protein domains can be used as effector models in MURPs. Examples are the following proteins as well as fragments of these proteins: cytokines, growth factors, enzymes, -receptors, micro-proteins, hormones, erythropoietin, adenosine deiminase, asparaginase, arginase, interferon, growth hormone, growth hormone releasing hormone, G-CSF, GM-CSF, insulin, hirudin, TNF-receptor, uricase, rasburicase, axokine, RNase, DNase, phosphatase, pseudomonas exotoxin, ricin, gelonin, desmoteplase, laronidase, thrombin, blood clotting enzyme, VEGF, protropin, somatropin, alteplase, interleukin, factor IIV, factor VIII, factor X, factor IX, dornase, glucocerebrosidase, follitropin, glucagon, thyrotropin, nesiritide, alteplase, teriparatide, agalsidase, laronidase, methioninase.

[0208] Protease-activated MURPs: To enhance the therapeutic index of an effector module, one can insert protease-labile sequences into URP sequences that are sensitive to proteases that are preferentially found in serum or in the target tissue to be treated by the MURP. This approach is illustrated in FIG. 9. Some designs allow one to construct proteins that are selectively activated when reaching a target tissue. Of particular interest are MURPs that are activated at a disease site. To facilitate such target-specific activation one can attach URP sequences in close proximity to the active site or receptor binding site of the effector module such that the resulting fusion protein has limited biological activity. Of particular interest is the activation of an effector module at a tumor site. Many tumor tissues express proteases in relatively high concentrations and sequences that are specifically cleaved by these tumor proteases can be inserted into URP sequences. For example, most prostate tumor tissues contain high concentrations of prostate specific antigen (PSA) which is a serine protease. Prodrugs consisting of a PSA-labile peptide conjugated to the cancer drug doxorubicin have shown selective activation in prostate tissue [DeFeo-Jones, D., et al. (2000) Nat Med, 6: 1248]. Of particular interest for disease-specific activation are proteins with cytostatic or cytotoxic activity like TNFalpha, and many cytokines and interleukins. Another application is the selective activation of proteins at the site of inflammation or at site of virus or bacterial infection.

[0209] Methods of production—MURPs containing URP sequences can be produced using molecular biology approaches that are well known in the art. A variety of cloning vectors are available for various expression systems like mammalian cells, yeast, and microbes. Of particular interest as expression hosts are *E. coli*, *S. cerevisiae*, *P. pastoris*, and chinese hamster ovary cells. Of particular interest are hosts that have been optimized to widen their codon usage. Of particular interest is a host that has been modified to enhance

expression of GRS. That can be done by providing DNA that encodes glycine-specific tRNAs. In addition, one can engineer the host such that loading of glycine-specific tRNAs is enhanced. The DNA encoding the enhanced protein can be operationally linked to a promoter sequence. The DNA encoding the enhanced protein as well as the operationally linked promoter can be part of a plasmid vector, viral vector or it can be inserted into the chromosome of the host.

[0210] For production one can culture the host under conditions that facilitate the production of the enhanced protein. Of particular interest are conditions that improve the production of GRS.

[0211] The subject MURPs can adopt a variety of formats. For instance, the MURPs can contain URPs that are fused to pharmaceutically active proteins to produce slow-release products. Such products can be injected or implanted locally for instance into or under the skin of a patient. Due to its large hydrodynamic radius the URP sequence-containing product is slowly released from the injection or implantation site which leads to a reduction of the frequency of injection or implantation. The URP sequences can be designed to contain regions that bind to cell surfaces or tissue in order to prolong the local retention of the drug at the injection site. Of particular interest are URP-containing products that can be formulated as soluble compounds but form aggregates or precipitates upon injection. This aggregation or precipitation can be triggered by a change in pH between the formulated product and the pH at the injection site. Alternatives are URP-containing products that precipitate or form aggregates as a result of a change in redox conditions. Yet another approach is a URP-containing product that is stabilized in solution by addition of non-active solutes, but that precipitates or aggregates upon injection as a result of diffusion of the solubilizing solutes. Another approach is to design URP-containing products that contain one or multiple Lysine or Cysteine residues in their URP sequence and that can be cross-linked prior to injection.

[0212] Where desired, the MURP is monomeric (here meaning not-crosslinked) when manufactured and formulated and when injected, but after subcutaneous injection the protein starts to crosslink with itself or with native human proteins, forming a polymer under the skin from which active drug molecules are freed only very gradually. Such release can be by disulfide bond reduction or disulfide shuffling as illustrated in FIG. 18, or it can be mediated by proteolysis as shown in FIG. 19, releasing active fragments into the circulation. It is important that these active fragments are large enough to have a long half-life, because the longer their secretion half-life, the lower the dose of the released protein can be, allowing the use of a lower dose of product to be injected or a longer time between injections.

[0213] One approach that offers these advantages is disulfide-mediated crosslinking of proteins. For example, a protein drug would be manufactured with a cyclic peptide in it (one or more). This cyclic peptide may or may not be involved in binding to the target. This protein is manufactured with the cyclic peptide formed, ie in oxidized form, to simplify purification. However, the product is then reduced and formulated to keep the protein in reduced form. It is important that the cyclic peptide reduces at a low concentration of reducing agent, such as 0.25, 0.5, 1.0, 2.0, 4.0 or 8.0 mM Dithiothreitol or Betamercaptoethanol or cysteine or equivalent reducing agent, so that the cyclic peptide can be reduced without reducing other disulfide containing protein modules in the product.

The use of FDA approved reducing agents is preferred, such as cysteine or glutathione. After subcutaneous injection, the low molecular weight reducing agent diffuses away rapidly or is neutralized by human proteins, exposing the drug to an oxidizing environment while it is still at a high molar concentration, which causes crosslinking of cysteines located on different protein chains, which leads to polymerization of the drug at the injection site. The longer the distance between the cysteines in the cyclic peptide, and the higher the concentration of the drug, the higher the degree of polymerization of the drug will be, since polymerization competes with cyclic peptide reformation. Over time, disulfide reduction and oxidation will cause disulfide reshuffling, which will lead to cyclic peptide reformation and monomerization and resolubilization of the drug. The release of the drug from the polymer can also occur via proteolysis which could be targeted and controlled or increased by building in cleavage sites for serum proteases. The crosslinking to the proteins could also be performed with a chemical protein-protein crosslinking agent, such as the ones listed in [table x]. Ideally, this is an already FDA-approved agent, such as those used for vaccine conjugation or conjugation of chemicals to proteins.

[0214] Instead of using disulfides, one can also stabilize proteins against proteolytic degradation using a wide variety of crosslinking agents. Most of the agents below are sold by Pierce Chemicals under that same name and instructions for their use are available online (www.piercenet.com). The agents that result in the same chain-to-chain distance as obtained with disulfides are the most likely to be useful for this application. The short-linker agents such as DFDNB are the most promising. The interchain distance can be readily determined from the structures of the chemicals as shown in www.piercenet.com.

[0215] There are a large number of specific chemical products that work based on the following small number of basic reaction schemes, all of which are described in detail at www.piercenet.com. Examples of useful crosslinking agents are Imidoesters, active halogens, maleimide, pyridyl disulfide, NHS-ester. Homobifunctional crosslinking agents have two identical reactive groups and are often used in a onestep chemical crosslinking procedure. Examples are BS3 (a non-cleavable water-soluble DSS analog), BSOE (base-reversible), DMA (Dimethyl adipimidate-2HCl), DMP (Dimethyl pimelimidate-2HCl), DMS (Dimethyl suberimidate-2HCl), DSG (5-carbon analog of DSS), DSP (Lomant's reagent), DSS (non-cleavable), DST (cleavable by oxidizing agents), DTBP (Dimethyl 3,3'-dithiobispropionimidate-2HCl), DTSSP, EGS, Sulfo-EGS, THPP, TSAT, DFDNB (1,5-Difluoro-2,4-dinitrobenzene) is especially useful for crosslinking between small spacial distances (Kornblatt, J. A. and Lake, D. F. (1980). Cross-linking of cytochrome oxidase subunits with difluorodinitrobenzene. *Can J. Biochem.* 58, 219-224).

[0216] Sulfhydryl-reactive homobifunctional crosslinking agents are homobifunctional protein crosslinkers that react with sulfhydryls are often based on maleimides, which react with —SH groups at pH 6.5-7.5, forming stable thioether linkages. BM[PEO]3 is an 8-atom polyether spacer that reduces potential for conjugate precipitation in sulfhydryl-to-sulfhydryl cross-linking applications. BM[PEO]4 is similar but with an 11-atom spacer. BMB is a non-cleavable crosslinker with a four-carbon spacer. BMDB makes a linkage that can be cleaved with periodate. BMH is a widely used homobifunctional sulfhydryl-reactive crosslinker. BMOE

has an especially short linker. DPDPB and DTME are cleavable crosslinkers. HVBS does not have the hydrolysis potential of maleimides. TMEA is another option. Hetero-bifunctional crosslinking agents have two different reactive groups. Examples are NHS-esters and amines/hydrazines via EDC activation, AEDP, ASBA (photoreactive, iodinated), EDC (water-soluble carbodiimide). Amine-Sulfhydryl reactive bifunctional crosslinkers are AMAS, APDP, BMPS, EMCA, EMCS, GMBS, KMUA, LC-SMCC, LC-SPDP, MBS, SBAP, SIA (extra short), SIAB, SMCC, SMPB, SMPH, SMPT, SPDP, Sulfo-EMCS, Sulfo-GMBS, Sulfo-KMUS, Sulfo-LC-SMPT, Sulfo-LC-SPDP, Sulfo-MBS, Sulfo-SIAB, Sulfo-SMCC, Sulfo-SMPB. Amino-group reactive heterobifunctional crosslinking agents are ANB-NOS, MSA, NHS-ASA, SADP, SAED, SAND, SANPAH, SASD, SFAD, Sulfo-HSAB, Sulfo-NHS-LC-ASA, Sulfo-SADP, Sulfo-SANPAH, TFCS.

[0217] A different slow release format has the drug labeled with a His6 tag, which is mixed and co-injected with Nickel-Nitrilotriacetic acid-conjugated beads (Ni-NTA beads), a GMO version of the ones that are available from Qiagen. The drug would slowly teach off the beads, providing depot and slow release as illustrated in FIG. 20. The beads are optional and can be replaced by a crosslinked, polymeric Nickel-nitrilotriacetic acid that leads to assembly of an even larger polymer.

[0218] URP sequences can contain sequences that are known to form multimers like alpha2D [Hill, R., et al. (1998) *J Am Chem Soc*, 120: 1138-1145] that was utilized to dimerize an antibody fragment [Kubetzko, S., et al. (2005) *Mol Pharmacol*, 68: 1439-54]. Examples of a useful homo dimerization peptide is the sequence SKVILFE. An example of useful heterodimerization sequences are the peptide ARARAR that can form dimers with the sequence DADADA and related sequences. Multimerization can improve the biological function of a molecule by increasing its avidity and it can influence pharmacokinetic properties and tissue distribution of the resulting MURPs.

[0219] "Multimerization modules" are amino acid sequences that facilitate dimer or multimer formation of MURPs. Multimerization modules may bind to themselves to form dimers or multimers. Alternatively, multimerization modules can bind to other modules of the MURP. These can be leucine zippers or small peptides like Hydra head activator derivatives (SKVILF-like) which forms antiparallel homopolymers, or peptides like RARARA and DADADA, which form high affinity antiparallel heteropolymers. Using one, two or more copies of these peptides one can force the formation of protein dimers, linear multimers or branched multimers.

[0220] The affinity of the association can be tailored by changing the type, length and composition of the peptides. Some applications require peptides that form homodimers as illustrated in FIG. 21. Other applications require heterodimers. In some cases, once associated, the peptides can be locked into place by forming disulfide bonds between the two protein chains, typically on either side of the peptides. Multimerization modules are useful for linking two MURP molecules together (head to tail, head to head, or tail to tail) as illustrated in FIG. 21. The multimerization modules can be located on either the N- or C-terminus in order to form dimers. If the multimerization modules are present at both termini, long, linear multimers will be formed. If more than two multimerization modules are present per protein, branched poly-

meric networks can be formed. The concepts of multimerization and chemical conjugation can be combined leading to useful for half-life extension and depot formation, leading to slow release of active drug from the depot or injection site as illustrated in FIG. 23.

[0221] The subject MURPs can incorporate a genetic or universal URP. One approach is to express a URP containing a long URP module, which provides half-life and contains multiple (typically 4-10) lysines (or other sites) that allows site-specific conjugation of peptides (ie linear, cyclic, 2SS, 3SS, etc) that bind to a specific target. The advantage of this approach is that the URP module is generic and can be conjugated with any target-specific peptide. Ideally the linkage of the target-specific peptide to the URP is a directed linkage, so that residues on the URP can only react with a residue on the target-specific peptide and exhaustive coupling can only produce a single species, which is a URP that is linked to a peptide at every lysine, for example. This complex behaves like a high-avidity multimer in its binding properties but is simple to manufacture. This approach is illustrated in FIG. 24.

[0222] The subject MURPs can also incorporate URPs to effect delivery across tissue barriers. URPs can be engineered to enhance delivery across the dermal, oral, buccal, intestinal, nasal, blood-brain, pulmonary, thecal, peritoneal, rectal, vaginal or many other tissue barriers.

[0223] One of the key obstacles to oral protein delivery is the sensitivity of most proteins to proteases in the digestive system. Conjugation to URP sequences can improve protease resistance of pharmaceutically active proteins and thus facilitate their uptake. It has been shown that protein uptake in the digestive system can be improved by adding molecular carriers. The main role of these carriers is an improvement of membrane permeability [Stoll, B. R., et al. (2000) *J Control Release*, 64: 217-28]. Thus one can include sequences into URP sequences that improve membrane permeability. Many sequences that improve membrane permeability are known and examples are sequences rich in arginine [Takenobu, T., et al. (2002) *Mol Cancer Ther*, 1: 1043-9]. Thus one can design URP sequences that improve cellular or oral uptake of proteins by combining two functions, a reduction in proteolytic degradation of the protein of interest as well as an increase in membrane permeability of the fusion product. Optional, one can add a sequence to the URP sequence that is sensitive to a protease that is preferentially located at in the target tissue for the drug of interest but is stable to proteases in the digestive tract. Examples of such URP sequences are sequences that contain long regions of GRS as well as sequences that are rich in basic amino acids in particular arginine and facilitate membrane transfer. URP can be utilized in a similar way to improve protein uptake via intranasal, intrapulmonary, or other routes of delivery.

SPECIFIC PRODUCT EXAMPLES

[0224] DR4/DR5 agonist—DR4 and DR5 are death receptors that are expressed on many tumor cells. These receptors can be triggered by trimerization which leads to cell death and tumor regression. Binding domains with specificity for DR4 or DR5 can be obtained by phage panning or other display methods. These DR4 or DR5-specific binding domains can be multimerized using URP modules as linkers as illustrated in FIG. 12. Of particular interest are MURPs that contain three or more binding modules with specificity for DR4 or DR5 or both. As illustrated in FIG. 12, MURPs can contain additional

binding modules with specificity for tumor antigens that are overexpressed in tumor tissues. This allows one to construct MURPs that specifically accumulate in tumor tissue and trigger cell death. MURPs can contain modules that bind either DR4 or DR5. Of particular interest are MURPs that contain binding modules that bind both DR4 and DR5.

[0225] Tumor-targeted Interleukin 2—Interleukin 2 (IL2) is a cytokine that can enhance the immune response to tumor tissue. However, systemic IL2 therapy is characterized by significant side effects. MURPs can be constructed that combine binding domains with specificity for tumor antigens and IL2 as effector module as illustrated in FIG. 13. Such MURP can selectively accumulate in tumor tissue and thus elicit a tumor-selective immune response while minimizing the systemic side effects of cytokine therapy. Such MURPs can target a variety of tumor antigens like EpCAM, Her2, CEA, EGFR, Thomsen Friedenreich antigen. Of particular utility are MURPs that bind to tumor antigens that show slow internalization. Similar MURPs can be designed using other cytokines or tumor necrosis factor- α as effector modules.

[0226] Tumor-selective asparaginase—Asparaginase is used to treat patients with acute leukemia. Both asparaginase from *E. coli* and asparaginase from *Erwinia* are used for treatment. Both enzymes can lead to immunogenicity and hypersensitive reactions. Oncaspar is PEGylated version of asparaginase that has reduced immunogenicity. However, the protein is difficult to manufacture and administered as a mixture of isomers. Adding URP sequences to termini and/or to internal loops allows the direct recombinant manufacture of an asparaginase variant that is homogeneous and has low immunogenicity. Various URP sequences and attachment sites can be compared to determine the optimum position for URP sequence attachment. Several other enzymes can degrade amino acids have reported antitumor activity. Examples are arginase, methioninase, phenylalanine ammonia lyase, and tryptophanase. Of particular interest is the phenylalanine ammonia lyase of *streptomyces maritimus*, which has a high specific activity and does not require a co-factor [Calabrese, J. C., et al. (2004) *Biochemistry*, 43: 11403-16]. Most of these enzymes are of bacterial or other non-human origin and are likely to elicit immune reactions. The immunogenicity of these enzymes can be reduced by adding one or more URP sequences. In addition, the therapeutic index and PK properties of these enzymes can be improved by increasing their hydrodynamic radius as a result of URP sequences attachment.

[0227] The subject MURPs can be designed to target any cellular proteins. A non-limiting list is provided below.

[0228] VEGF, VEGF-R1, VEGF-R2, VEGF-R3, Her-1, Her-2, Her-3, EGF-1, EGF-2, EGF-3, Alpha3, cMet, ICOS, CD40L, LFA-1, c-Met, ICOS, LFA-1, IL-6, B7.1, B7.2, OX40, IL-1b, TACI, IgE, BAFF or BLys, TPO-R, CD19, CD20, CD22, CD33, CD28, IL-1-R1, TNF α , TRAIL-R1, Complement Receptor 1, FGFR, Osteopontin, Vitronectin, Ephrin A1-A5, Ephrin B1-B3, alpha-2-macroglobulin, CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CCL13, CCL14, CCL15, CXCL16, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, PDGF, TGF β , GM-CSF, SCF, p40 (IL12/IL23), IL1b, IL1a, IL1ra, IL2, IL3, IL4, IL5, IL6, IL8, IL10, IL12, IL15, IL23, Fas, FasL, Flt3 ligand, 41BB, ACE, ACE-2, KGF, FGF-7, SCF, Netrin1,2, IFN α ,b,g, Caspase2,3,7,8,10, ADAM S1,S5,8,9,15,TS1,TS5; Adiponectin, ALCAM, ALK-1, APRIL, Annexin V, Angiogenin, Amphiregulin,

Angiopoietin1,2,4, B7-1/CD80, B7-2/CD86, B7-H1, B7-H2, B7-H3, Bcl-2, BACE-1, BAK, BCAM, BDNF, bNGF, bECGF, BMP2,3,4,5,6,7,8; CRP, Cadherin6,8,11; Cathepsin A,B,C,D,E,L,S,V,X; CD11a/LFA-1, LFA-3, GP2b3a, GH receptor, RSV F protein, IL-23 (p40, p19), IL-12, CD80, CD86, CD28, CTLA-4, $\alpha\beta 1$, $\alpha\beta 7$, TNF/Lymphotoxin, IgE, CD3, CD20, IL-6, IL-6R, BLYS/BAFF, IL-2R, HER2, EGFR, CD33, CD52, Digoxin, Rho (D), Varicella, Hepatitis, CMV, Tetanus, Vaccinia, Antivenom, Botulinum, Trail-R1, Trail-R2, cMet, TNF-R family, such as LA NGF-R, CD27, CD30, CD40, CD95, Lymphotoxin a/b receptor, Wsl-1, TL1A/TNFSF15, BAFF, BAFF-R/TNFSF13C, TRAIL R2/TNFSF10B, TRAIL R2/TNFSF10B, Fas/TNFSF6 CD27/TNFSF7, DR3/TNFSF25, HVEM/TNFSF14, TROY/TNFSF19, CD40 Ligand/TNFSF5, BCMA/TNFSF17, CD30/TNFSF8, LIGHT/TNFSF14, 4-1BB/TNFSF9, CD40/TNFSF5, GITR/TNFSF18, Osteoprotegerin/TNFSF11B, RANK/TNFSF11A, TRAIL R3/TNFSF10C, TRAIL/TNFSF10, TRANCE/RANK L/TNFSF11, 4-1BB Ligand/TNFSF9, TWEAK/TNFSF12, CD40 Ligand/TNFSF5, Fas Ligand/TNFSF6, RELT/TNFSF19L, APRIL/TNFSF13, DcR3/TNFSF6B, TNF RI/TNFSF1A, TRAIL R1/TNFSF10A, TRAIL R4/TNFSF10D, CD30 Ligand/TNFSF8, GITR Ligand/TNFSF18, TNFSF18, TACI/TNFSF13B, NGF R/TNFSF16, OX40 Ligand/TNFSF4, TRAIL R2/TNFSF10B, TRAIL R3/TNFSF10C, TWEAK R/TNFSF12, BAFF/BLYS/TNFSF13, DR6/TNFSF21, TNF-alpha/TNFSF1A, Pro-TNF-alpha/TNFSF1A, Lymphotoxin beta R/TNFSF3, Lymphotoxin beta R (LTbR)/Fc Chimera, TNF RI/TNFSF1A, TNF-beta/TNFSF1B, PGRP-S, TNF RI/TNFSF1A, TNF RII/TNFSF1B, EDA-A2, TNF-alpha/TNFSF1A, EDAR, XEDAR, TNF RI/TNFSF1A.

[0229] Of particular interest are human target proteins that are commercially available in purified form. Examples are: 4EBP1, 14-3-3 zeta, 53BP1, 2B4/SLAMF4, CCL21/6CKine, 4-1BB/TNFSF9, 8D6A, 4-1BB Ligand/TNFSF9, 8-oxodG, 4-Amino-1,8-naphthalimide, A2B5, Aminopeptidase LRAP/ERAP2, A33, Aminopeptidase N/ANPEP, Aag, Aminopeptidase P2/XPNPEP2, ABCG2, Aminopeptidase P1/XPNPEP1, ACE, Aminopeptidase PILS/ARTS1, ACE-2, Amnionless, Actin, Amphiregulin, beta-Actin, AMPK alpha 1/2, Activin A, AMPK alpha 1, Activin AB, AMPK alpha 2, Activin B, AMPK beta 1, Activin C, AMPK beta 2, Activin RIA/ALK-2, Androgen R/NR3C4, Activin RIB/ALK-4, Angiogenin, Activin RIIA, Angiopoietin-1, Activin RIIb, Angiopoietin-2, ADAM8, Angiopoietin-3, ADAM9, Angiopoietin-4, ADAM10, Angiopoietin-like 1, ADAM12, Angiopoietin-like 2, ADAM15, Angiopoietin-like 3, TACE/ADAM17, Angiopoietin-like 4, ADAM19, Angiopoietin-like 7/CDT6, ADAM33, Angiostatin, ADAMTS4, Annexin A1/Annexin I, ADAMTS5, Annexin A7, ADAMTS1, Annexin A10, ADAMTSL-1/Punctin, Annexin V, Adiponectin/Acrp30, ANP, AEBSE, AP Site, Aggregran, APAF-1, Agrin, APC, AgRP, APE, AGTR-2, APJ, AIF, APLP-1, Akt, APLP-2, Akt1, Apolipoprotein AI, Akt2, Apolipoprotein B, Akt3, APP, Serum Albumin, APRIL/TNFSF13, ALCAM, ARC, ALK-1, Artemin, ALK-7, Arylsulfatase A/ARSA, Alkaline Phosphatase, ASAH2/N-acylsphingosine Amidohydrolase-2, alpha 2u-Globulin, ASC, alpha-1-Acid Glycoprotein, ASGR1, alpha-Fetoprotein, ASK1, ALS, ATM, Ameloblastin, ATRIP, AMICA/JAML, Aurora A, AMIGO, Aurora B, AMIGO2, Axin-1, AMIGO3, Ax1, Aminoacylase/ACY1, Azurocidin/CAP37/HBP, Aminopeptidase A/ENPEP,

B4GALT1, BIM, B7-1/CD80, 6-Biotin-17-NAD, B7-2/CD86, BLAME/SLAMF8, B7-H1/PD-L1, CXCL13/BLC/BCA-1, B7-H2, BLIMP1, B7-H3, Blk, B7-H4, BMI-1, BACE-1, BMP-1/PCP, BACE-2, BMP-2, Bad, BMP-3, BAFF/TNFSF13B, BMP-3b/GDF-10, BAFF R/TNFSF13C, BMP-4, Bag-1, BMP-5, BAK, BMP-6, BAMBI/NMA, BMP-7, BARD1, BMP-8, Bax, BMP-9, BCAM, BMP-10, Bcl-10, BMP-15/GDF-9B, Bcl-2, BMPRI/ALK-3, Bcl-2 related protein A1, BMPRI/ALK-6, Bcl-w, BMPRII, Bcl-x, BNIP3L, Bcl-xL, BOC, BCMA/TNFSF17, BOK, BDNF, BPDE, Benzamide, Brachyury, Common beta Chain, B-Raf, beta IG-H3, CXCL14/BRAK, Betacellulin, BRCA1, beta-Defensin 2, BRCA2, BID, BTLA, Biglycan, Bub-1, Bik-like Killer Protein, c-jun, CD90/Thy1, c-Rel, CD94, CCL6/C10, CD97, C1q R1/CD93, CD151, C1qTNF1, CD160, C1qTNF4, CD163, C1qTNF5, CD164, Complement Component C1r, CD200, Complement Component C1s, CD200 R1, Complement Component C2, CD229/SLAMF3, Complement Component C3a, CD23/Fc epsilon RII, Complement Component C3d, CD2F-10/SLAMF9, Complement Component C5a, CD5L, Cadherin-4/R-Cadherin, CD69, Cadherin-6, CDC2, Cadherin-8, CDC25A, Cadherin-11, CDC25B, Cadherin-12, CDCP1, Cadherin-13, CDO, Cadherin-17, CDX4, E-Cadherin, CEACAM-1/CD66a, N-Cadherin, CEACAM-6, P-Cadherin, Cerberus 1, VE-Cadherin, CFTR, Calbindin D, cGMP, Calcineurin A, Chem R23, Calcineurin B, Chemerin, Calreticulin-2, Chemokine Sampler Packs, CaM Kinase II, Chitinase 3-like 1, cAMP, Chitotriosidase/CHIT1, Cannabinoid R1, Chk1, Cannabinoid R2/CB2/CNR2, Chk2, CAR/NR13, CHL-1/L1CAM-2, Carbonic Anhydrase J, Choline Acetyltransferase/ChAT, Carbonic Anhydrase II, Chondrolectin, Carbonic Anhydrase III, Chordin, Carbonic Anhydrase IV, Chordin-Like 1, Carbonic Anhydrase VA, Chordin-Like 2, Carbonic Anhydrase VB, CINC-1, Carbonic Anhydrase VI, CINC-2, Carbonic Anhydrase VII, CINC-3, Carbonic Anhydrase VIII, Claspin, Carbonic Anhydrase IX, Claudin-6, Carbonic Anhydrase X, CLC, Carbonic Anhydrase XII, CLEC-1, Carbonic Anhydrase XIII, CLEC-2, Carbonic Anhydrase XIV, CLECSF13/CLECSF4F, Carboxymethyl Lysine, CLECSF8, Carboxypeptidase A1/CPA1, CLF-1, Carboxypeptidase A2, CL-P1/COLEC12, Carboxypeptidase A4, Clusterin, Carboxypeptidase B1, Clusterin-like 1, Carboxypeptidase E/CPE, CMG-2, Carboxypeptidase XI, CMV UL146, Cardiotrophin-1, CMV UL147, Carnosine Dipeptidase 1, CNP, Caronte, CNTF, CART, CNTF R alpha, Caspase, Coagulation Factor II/Thrombin, Caspase-1, Coagulation Factor III/Tissue Factor, Caspase-2, Coagulation Factor VII, Caspase-3, Coagulation Factor X, Caspase-4, Coagulation Factor XI, Caspase-6, Coagulation Factor XIV/Protein C, Caspase-7, COCO, Caspase-8, Cohesin, Caspase-9, Collagen I, Caspase-10, Collagen II, Caspase-12, Collagen IV, Caspase-13, Common gamma Chain/IL-2 R gamma, Caspase Peptide Inhibitors, COMP/Thrombospondin-5, Catalase, Complement Component C1rLP, beta-Catenin, Complement Component C1qA, Cathepsin 1, Complement Component C1qC, Cathepsin 3, Complement Factor D, Cathepsin 6, Complement Factor I, Cathepsin A, Complement MASP3, Cathepsin B, Connexin 43, Cathepsin C/DPPI, Contactin-1, Cathepsin D, Contactin-2/TAG1, Cathepsin E, Contactin-4, Cathepsin F, Contactin-5, Cathepsin H, Corin, Cathepsin L, Cornulin, Cathepsin O, CORS26/C1qTNF, 3, Cathepsin S, Rat Cortical Stem Cells, Cathepsin V, Cortisol, Cathepsin X/Z/P, COUP-TF I/NR2F1, CBP, COUP-TF

II/NR2F2, CCI, COX-1, CCK-A R, COX-2, CCL28, CRACC/SLAMF7, CCR1, C-Reactive Protein, CCR2, Creatine Kinase, Muscle/CKMM, CCR3, Creatinine, CCR4, CREB, CCR5, CREG, CCR6, CRELD1, CCR7, CRELD2, CCR8, CRHBP, CCR9, CRHR-1, CCR10, CRIM1, CD155/PVR, Cripto, CD2, CRISP-2, CD3, CRISP-3, CD4, Crossveinless-2, CD4+/45RA-, CRTAM, CD4+/45RO-, CRTH-2, CD4+/CD62L-/CD44, CRY1, CD4+/CD62L+/CD44, Cryptic, CD5, CSB/ERCC6, CD6, CCL27/CTACK, CD8, CTGF/CCN2, CD8+/45RA-, CTLA-4, CD8+/45RO-, Cubilin, CD9, CX3CR1, CD14, CXADR, CD27/TNFRSF7, CXCL16, CD27 Ligand/TNFSF7, CXCR3, CD28, CXCR4, CD30/TNFRSF8, CXCR5, CD30 Ligand/TNFSF8, CXCR6, CD31/PECAM-1, Cyclophilin A, CD34, Cyr61/CCN1, CD36/SR-B3, Cystatin A, CD38, Cystatin B, CD40/TNFRSF5, Cystatin C, CD40 Ligand/TNFSF5, Cystatin D, CD43, Cystatin E/M, CD44, Cystatin F, CD45, Cystatin H, CD46, Cystatin H2, CD47, Cystatin S, CD48/SLAMF2, Cystatin SA, CD55/DAF, Cystatin SN, CD58/LFA-3, Cytochrome c, CD59, Apocytocytocrome c, CD68, Holocytochrome c, CD72, Cytokeratin 8, CD74, Cytokeratin 14, CD83, Cytokeratin 19, CD84/SLAMF5, Cytonin, D6, DSP1, DAN, Dkk-1, DANCE, Dkk-2, DARPP-32, Dkk-3, DAX1/NR0B1, Dkk-4, DCC, DLEC, DCIR/CLEC4A, DLL1, DCAR, DLL4, DCR3/TNFRSF6B, d-Luciferin, DC-SIGN, DNA Ligase IV, DC-SIGNR/CD299, DNA Polymerase beta, DcTRAIL R1/TNFRSF23, DNAM-1, DcTRAIL R2/TNFRSF22, DNAPKcs, DDR1, DNER, DDR2, Dopa Decarboxylase/DDC, DEC-205, DPCR-1, Decapentaplegic, DPP6, Decorin, DPPA4, Dectin-1/CLEC7A, DPPA5/ESG1, Dectin-2/CLEC6A, DPPII/QPP/PPP7, DEP-1/CD148, DPPIV/CD26, Desert Hedgehog, DR3/TNFRSF25, Desmin, DR6/TNFRSF21, Desmoglein-1, DSCAM, Desmoglein-2, DSCAM-L1, Desmoglein-3, DSPG3, Dishevelled-1, Dtk, Dishevelled-3, Dynamamin, EAR2/NR2F6, EphA5, ECE-1, EphA6, ECE-2, EphA7, ECF-L/CHI3L3, EphA8, ECM-1, EphB1, Ecotin, EphB2, EDA, EphB3, EDA-A2, EphB4, EDAR, EphB6, EDG-1, Ephrin, EDG-5, Ephrin-A1, EDG-8, Ephrin-A2, eEF-2, Ephrin-A3, EGF, Ephrin-A4, EGF R, Ephrin-A5, EGR1, Ephrin-B, EG-VEGF/PK1, Ephrin-B1, eIF2 alpha, Ephrin-B2, eIF4E, Ephrin-B3, Elk-1, Epigen, EMAP-II, Epi-morphin/Syntaxin 2, EMMPRIN/CD147, Epiregulin, CXCL5/ENA, EPR-1/Xa Receptor, Endocan, ErbB2, Endoglin/CD105, ErbB3, Endoglycan, ErbB4, Endonuclease III, ERCC1, Endonuclease IV, ERCC3, Endonuclease V, ERK1/ERK2, Endonuclease VIII, ERK1, Endorepellin/Perlecan, ERK2, Endostatin, ERK3, Endothelin-1, ERK5/BMK1, Engrailed-2, ERR alpha/NR3B1, EN-RAGE, ERR beta/NR3B2, Enteropeptidase/Enterokinase, ERR gamma/NR3B3, CCL11/Eotaxin, Erythropoietin, CCL24/Eotaxin-2, Erythropoietin R, CCL26/Eotaxin-3, ESAM, EpCAM/TROP-1, ER alpha/NR3A1, EPCR, ER beta/NR3A2, Eph, Exonuclease III, EphA1, Exostosin-like 2/EXTL2, EphA2, Exostosin-like 3/EXTL3, EphA3, FABP1, FGF-BP, FABP2, FGF R1-4, FABP3, FGF R1, FABP4, FGF R2, FABP5, FGF R3, FABP7, FGF R4, FABP9, FGF R5, Complement Factor B, Fgr, FADD, FHR5, FAM3A, Fibronectin, FAM3B, Ficolin-2, FAM3C, Ficolin-3, FAM3D, FITC, Fibroblast Activation Protein alpha/FAP, FKBP38, Fas/TNFRSF6, Flap, Fas Ligand/TNFSF6, FLIP, FATP1, FLRG, FATP4, FLRT1, FATP5, FLRT2, Fc gamma RI/CD64, FLRT3, Fc gamma RII/CD32b, Fc gamma RIIc/CD32c, Fc gamma RIII/CD16, Fc gamma RIIIA/CD32a, Follistatin, Fc gamma RIIIB/CD16, Follistatin-like 1, FcRH1/IRTA5, FosB/GOS3, FcRH2/IRTA4,

FoxD3, FcRH4/IRTA1, FoxJ1, FcRH5/IRTA2, FoxP3, Fc Receptor-like 3/CD16-2, Fpg, FEN-1, FPR1, Fetuin A, FPRL1, Fetuin B, FPRL2, FGF acidic, CX3CL1/Fractalkine, FGF basic, Frizzled-1, FGF-3, Frizzled-2, FGF-4, Frizzled-3, FGF-5, Frizzled-4, FGF-6, Frizzled-5, FGF-8, Frizzled-6, FGF-9, Frizzled-7, FGF-10, Frizzled-8, FGF-11, Frizzled-9, FGF-12, Frk, FGF-13, sFRP-1, FGF-16, sFRP-2, FGF-17, sFRP-3, FGF-19, sFRP-4, FGF-20, Furin, FGF-21, FXR/NR1H4, FGF-22, Fyn, FGF-23, G9a/EHMT2, GFR alpha-3/GDNF R alpha-3, GABA-A-R alpha 1, GFR alpha-4/GDNF R alpha-4, GABA-A-R alpha 2, GTR/TNFRSF18, GABA-A-R alpha 4, GTR Ligand/TNFSF18, GABA-A-R alpha 5, GLI-1, GABA-A-R alpha 6, GLI-2, GABA-A-R beta 1, GLP/EHMT1, GABA-A-R beta 2, GLP-1 R, GABA-A-R beta 3, Glucagon, GABA-A-R gamma 2, Glucosamine (N-acetyl)-6-Sulfatase/GNS, GABA-B-R2, GluR1, GAD1/GAD67, GluR2/3, GAD2/GAD65, GluR2, GADD45 alpha, GluR3, GADD45 beta, Glut1, GADD45 gamma, Glut2, Galectin-1, Glut3, Galectin-2, Glut4, Galectin-3, Glut5, Galectin-3 BP, Glutaredoxin 1, Galectin-4, Glycine R, Galectin-7, Glycophorin A, Galectin-8, Glypican 2, Galectin-9, Glypican 3, GalNAc4S-6ST, Glypican 5, GAP-43, Glypican 6, GAPDH, GM-CSF, Gas1, GM-CSF R alpha, Gas6, GMF-beta, GASP-1/WFIKKRNP, gp130, GASP-2/WFIKKRNP; Glycogen Phosphorylase BB/GPBB, GATA-1, GPR15, GATA-2, GPR39, GATA-3, GPVI, GATA-4, GR/NR3C1, GATA-5, Gr-1/Ly-6G, GATA-6, Granulysin, GBL, Granzyme A, GCNF/NR6A1, Granzyme B, CXCL6/GCP-2, Granzyme D, G-CSF, Granzyme G, G-CSF R, Granzyme H, GDF-1, GRASP, GDF-3 GRB2, GDF-5, Gremlin, GDF-6, GRO, GDF-7, CXCL1/GRO alpha, GDF-8, CXCL2/GRO beta, GDF-9, CXCL3/GRO gamma, GDF-11, Growth Hormone, GDF-15, Growth Hormone R, GDNF, GRP75/HSPA9B, GFAP, GSK-3 alpha/beta, GFI-1, GSK-3 alpha, GFR alpha-1/GDNF R alpha-1, GSK-3 beta, GFR alpha-2/GDNF R alpha-2, EZF1T, H2AX, Histidine, H60, HM74A, HAI-1, HMG2A, HAI-2, HMGB1, HAI-2A, TCF-2/HNF-1 beta, HAI-2B, HNF-3 beta/FoxA2, HAND1, HNF-4 alpha/NR2A1, HAPLN1, HNF-4 gamma/NR2A2, Airway Trypsin-like Protease/HAT, HO-1/HMOX1/HSP32, HB-EGF, HO-2/HMOX2, CCL14a/HCC-1, HPRG, CCL14b/HCC-3, Hrk, CCL16/HCC-4, HRP-1, alpha HCG, HS6ST2, Hck, HSD-1, HCR/CRAM-A/B, HSD-2, HDGF, HSP10/EPF, Hemoglobin, HSP27, Hepassocin, HSP60, HES-1, HSP70, HES-4, HSP90, HGF, HTRA/Protease Do, HGF Activator, HTRA1/PRSS11, HGF R, HTRA2/Omi, HIF-1 alpha, HVEM/TNFRSF14, HIF-2 alpha, Hyaluronan, HIN-1/Secretoglobulin 3A1, 4-Hydroxynonenal, Hip, CCL1/I-309/TCA-3, IL-10, cIAP (pan), IL-10 R alpha, cIAP-1/HIAP-2, IL-10 R beta, cIAP-2/HIAP-1, IL-1, IBSP/Sialoprotein II, IL-11 R alpha, ICAM-1/CD54, IL-12, ICAM-2/CD102, IL-12/IL-23 p40, ICAM-3/CD50, IL-12 R beta 1, ICAM-5, IL-12 R beta 2, ICAT, IL-13, ICOS, IL-13 R alpha 1, Iduronate 2-Sulfatase/IDS, IL-13 R alpha 2, IFN, IL-15, IFN-alpha, IL-15 R alpha, IFN-alpha 1, IL-16, IFN-alpha 2, IL-17, IFN-alpha 4b, IL-17 R, IFN-alpha A, IL-17 RC, IFN-alpha B2, IL-17 RD, IFN-alpha C, IL-17B, IFN-alpha D, IL-17B R, IFN-alpha F, IL-17C, IFN-alpha G, IL-17D, IFN-alpha H2, IL-17E, IFN-alpha I, IL-17F, IFN-alpha J1, IL-18/IL-1F4, IFN-alpha K, IL-18 BP, IFN-alpha WA, IL-18 BPC, IFN-alpha/beta R1, IL-18 BPd, IFN-alpha/beta R2, IL-18 R alpha/IL-1 R5, IFN-beta, IL-18 R beta/IL-1 R7, IFN-gamma, IL-19, IFN-gamma R1, IL-20, IFN-gamma R2, IL-20 R alpha, IFN-omega, IL-20 R beta, IgE, IL-21, IGFBP-1, IL-21 R, IGFBP-2, IL-22,

IGFBP-3, IL-22 R, IGFBP-4, IL-22BP, IGFBP-5, IL-23, IGFBP-6, IL-23 R, IGFBP-L1, IL-24, IGFBP-rp1/IGFBP-7, IL-26/AK155, IGFBP-rp10, IL-27, IGF-I, IL-28A, IGF-I R, IL-28B, IGF-II, IL-29/IFN-lambda 1, IGF-II R, IL-31, IgG, IL-31 RA, IgM, IL-32 alpha, IGSF2, IL-33, IGSF4A/SynCAM, ILT2/CD85j, IGSF4B, ILT3/CD85k, IGSF8, ILT4/CD85d, IgY, ILT5/CD85a, Ikb-beta, ILT6/CD85e, IKK alpha, Indian Hedgehog, IKK epsilon, INSRR, IKK gamma, Insulin, IL-1 alpha/IL-1F1, Insulin R/CD220, IL-1 beta/IL-1F2, Proinsulin, IL-1ra/IL-1F3, Insulysin/IDE, IL-1F5/FIL1 delta, Integrin alpha 2/CD49b, IL-1F6/FIL1 epsilon, Integrin alpha 3/CD49c, IL-1F7/FIL1 zeta, Integrin alpha 3 beta 1/VLA-3, IL-1F8/FIL1 eta, Integrin alpha 4/CD49d, IL-1F9/IL-1H1, Integrin alpha 5/CD49e, IL-1F10/IL-1HY2, Integrin alpha 5 beta 1, IL-1 RI, Integrin alpha 6/CD49f, IL-1 RII, Integrin alpha 7, IL-1 R3/IL-1 R AcP, Integrin alpha 9, IL-1 R4/ST2, Integrin alpha E/CD103, IL-1 R6/IL-1 R rp2, Integrin alpha L/CD11a, IL-1 R8, Integrin alpha L beta 2, IL-1 R9, Integrin alpha M/CD11b, IL-2, Integrin alpha M beta 2, IL-2 R alpha, Integrin alpha V/CD51, IL-2 R beta, Integrin alpha V beta 5, IL-3, Integrin alpha V beta 3, IL-3 R alpha, Integrin alpha V beta 6, IL-3 R beta, Integrin alpha X/CD11c, IL-4, Integrin beta 1/CD29, IL-4 R, Integrin beta 2/CD18, IL-5, Integrin beta 3/CD61, IL-5 R alpha, Integrin beta 5, IL-6, Integrin beta 6, IL-6 R, Integrin beta 7, IL-7, CXCL10/IP-10/CRG-2, IL-7 R alpha/CD127, IRAK1, CXCR1/IL-8 RA, IRAK4, CXCR2/IL-8 RB, IRS-1, CXCL8/IL-8, Islet-1, IL-9, CXCL11/I-TAC, IL-9 R, Jagged 1, JAM-4/IGSF5, Jagged 2, JNK, JAM-A, JNK1/JNK2, JAM-B/VE-JAM, JNK1, JAM-C, JNK2, Kininogen, Kallikrein 3/PSA, Kininostatin, Kallikrein 4, KIR/CD158, Kallikrein 5, KIR2DL1, Kallikrein 6/Neurosin, KIR2DL3, Kallikrein 7, KIR2DL4/CD158d, Kallikrein 8/Neurosin, KIR2DS4, Kallikrein 9, KIR3DL1, Plasma Kallikrein/KLK1, KIR3DL2, Kallikrein 10, Kirrel2, Kallikrein 11, KLF4, Kallikrein 12, KLF5, Kallikrein 13, KLF6, Kallikrein 14, Klotho, Kallikrein 15, Klotho beta, KC, KOR, Keap1, Kremen-1, Kell, Kremen-2, KGF/FGF-7, LAG-3, LINGO-2, LAIR1, Lipin 2, LAIR2, Lipocalin-1, Laminin alpha 4, Lipocalin-2/NGAL, Laminin gamma 1, 5-Lipoxygenase, Laminin I, LXR alpha/NR1H3, Laminin S, LXR beta/NR1H2, Laminin-1, Livin, Laminin-5, LIX, LAMP, LMIR1/CD300A, Langerin, LMIR2/CD300c, LAR, LMIR3/CD300LF, Latexin, LMIR5/CD300LB, Layilin, LMIR6/CD300LE, LBP, LMO2, LDL R, LOX-1/SR-E1, LECT2, LRH-1/NR5A2, LEDGF, LRIG1, Lefty, LRIG3, Lefty-1, LRP-1, Lefty-A, LRP-6, Legumain, LSECtin/CLEC4G, Leptin, Lumican, Leptin R, CXCL15/Lungkine, Leukotriene B4, XCL1/Lymphotoxin, Leukotriene B4 R1, Lymphotoxin, LIF, Lymphotoxin beta/TNFSF3, LIF R alpha, Lymphotoxin beta R/TNFSF3, LIGHT/TNFSF14, Lyn, Limitin, Lyp, LIMPII/SR-B2, Lysyl Oxidase Homolog 2, LIN-28, LYVE-1, LINGO-1, alpha 2-Macroglobulin, CXCL9/MIG, MAD2L1, Mimecan, MadCAM-1, Mindin, MafB, Mineralocorticoid R/NR3C2, MafF, CCL3L1/MIP-1 alpha Isoform LD78 beta, MafG, CCL3/MIP-1 alpha, MafK, CCL4L1/LAG-1, MAG/Siglec-4a, CCL4/MIP-1 beta, MANF, CCL15/MIP-1 delta, MAP2, CCL9/10/MIP-1 gamma, MAPK, MIP-2, Marapsin/Pancreasin, CCL19/MIP-3 beta, MARCKS, CCL20/MIP-3 alpha, MARCO, MIP-1, Mash1, MIP-II, Matrilin-2, MIP-III, Matrilin-3, MIS/AMH, Matrilin-4, MIS RII, Matrilin-4, MIXL1, MBL, MKK3/MKK6, MBL-2, MKK3, Melanocortin 3R/MC3R, MKK4, MCAM/CD146, MKK6, MCK-2, MKK7, Mcl-1, MKP-3, MCP-6, MLH-1, CCL2/MCP-1, MLK4 alpha,

MCP-11, MMP, CCL8/MCP-2, MMP-1, CCL7/MCP-3/MARC, MMP-2, CCL13/MCP-4, MMP-3, CCL12/MCP-5, MMP-7, M-CSF, MMP-8, M-CSF R, MMP-9, MCV-type 11, MMP-10, MD-1, MMP-11, MD-2; MMP-12, CCL22/MDC, MMP-13, MDL-1/CLEC5A, MMP-14, MDM2, MMP-15, MEA-1, MMP-16/MT3-MMP, MEK1/MEK2, MMP-24/MT5-MMP, MEK1, MMP-25/MT6-MMP, MEK2, MMP-26, Melusin, MMR, MEPE, MOG, Meprin alpha, CCL23/MPIF-1, Meprin beta, M-Ras/R-Ras3, Mer, Mre11, Mesothelin, MRP1 Meteorin, MSK1/MSK2, Methionine Aminopeptidase 1, MSK1, Methionine Aminopeptidase, MSK2, Methionine Aminopeptidase 2, MSP, MFG-E8, MSP R/Ron, MFRP, Mug, MgcRacGAP, MULT-1, MGL2, Musashi-1, MGMT, Musashi-2, MIA, MuSK, MICA, MutY DNA Glycosylase, MICB, MyD88, MICL/CLEC12A, Myeloperoxidase, beta 2 Microglobulin, Myocardin, Midkine, Myocilin, MIF, Myoglobin, NAIP NGFI-B gamma/NR4A3, Nanog, NgR2/NgRH1, CXCL7/NAP-2, NgR3/NgRH2, Nbs1, Nidogen-1/Entactin, NCAM-1/CD56, Nidogen-2, NCAM-L1, Nitric Oxide, Nectin-1, Nitrotyrosine, Nectin-2/CD112, NKG2A, Nectin-3, NKG2C, Nectin-4, NKG2D, Neogenin, NKp30, Neprilysin/CD10, NKp44, Neprilysin-2/MMEL1/MMEL2, NKp46/NCR1, Nestin, NKp80/KLRF1, NETO2, NKX2.5, Netrin-1, NMDA R, NR1 Subunit, Netrin-2, NMDA R, NR2A Subunit, Netrin-4, NMDA R, NR2B Subunit, Netrin-G1a, NMDA R, NR2C Subunit, Netrin-G2a, N-Me-6,7-diOH-TIQ, Neuregulin-1/NRG1, Nodal, Neuregulin-3/NRG3, Noggin, Neuritin, Nogo Receptor, NeuroD1, Nogo-A, Neurofascin, NOMO, Neurogenin-1, Nope, Neurogenin-2, Norrin, Neurogenin-3, eNOS, Neurolysin, iNOS, Neuropophysin II, nNOS, Neuropilin-1, Notch-1, Neuropilin-2, Notch-2, Neuropoietin, Notch-3, Neurotrimin, Notch-4, Neurturin, NOV/CCN3, NFAM1, NRAGE, NF-H, NrCAM, NFkB1, NRL, NFkB2, NT-3, NF-L, NT-4, NF-M, NTB-A/SLAMF6, NG2/MCSP, NTH1, NGF R/TNFRSF16, Nucleostemin, beta-NGF, Nurr-1/NR4A2, NGFI-B alpha/NR4A1, OAS2, Orexin B, OBCAM, OSCAR, OCAM, OSF-2/Periostin, OCIL/CLEC2d, Oncostatin M/OSM, OCILRP2/CLEC21, OSM R beta, Oct-3/4, Osteoactivin/GPNMB, OGG1, Osteoadherin, Olig 1, 2, 3, Osteocalcin, Olig1, Osteocrin, Olig2, Osteopontin, Olig3, Osteoprotegerin/TNFRSF11B, Oligodendrocyte Marker O1, Otx2, Oligodendrocyte Marker O4, OV-6, OMgp, OX40/TNFRSF4, Opticin, OX40 Ligand/TNFSF4, Orexin A, OAS2, Orexin B, OBCAM, OSCAR, OCAM, OSF-2/Periostin, OCIL/CLEC2d, Oncostatin M/OSM, OCILRP2/CLEC2i, OSM R beta, Oct-3/4, Osteoactivin/GPNMB, OGG1, Osteoadherin, Olig 1, 2, 3, Osteocalcin, Olig1, Osteocrin, Olig2, Osteopontin, Olig3, Osteoprotegerin/TNFRSF11B, Oligodendrocyte Marker O1, Otx2, Oligodendrocyte Marker O4, OV-6, OMgp, OX40/TNFRSF4, Opticin, OX40 Ligand/TNFSF4, Orexin A, RACK1, Ret, Rad1, REV-ERB alpha/NR1D1, Rad17, REV-ERB beta/NR1D2, Rad51, Rex-1, Rae-1, RGM-A, Rae-1 alpha, RGM-B, Rae-1 beta, RGM-C, Rae-1 delta, Rheb, Rae-1 epsilon, Ribosomal Protein S6, Rae-1 gamma, RIP1, Raf-1, ROBO1, RAGE, ROBO2, Ra1A/Ra1B, ROBO3, Ra1A, ROBO4, Ra1B, ROR/NR1F1-3 (pan), RANK/TNFRSF11A, ROR alpha/NR1F1, CCL5/RANTES, ROR gamma/NR1F3, Rap1A/B, RTK-like Orphan Receptor 1/ROR1, RAR alpha/NR1B1, RTK-like Orphan Receptor 2/ROR2, RAR beta/NR1B2, RP105, RAR gamma/NR1B3, RPA2, Ras, RSK (pan), RBP4, RSK1/RSK2, RECK, RSK1, Reg 2/PAP, RSK2, Reg I, RSK3, Reg II, RSK4, Reg III, R-Spondin 1, Reg IIIa, R-Spondin 2, Reg IV, R-Spondin 3,

Relaxin-1, RUNX1/CBFA2, Relaxin-2, RUNX2/CBFA1, Relaxin-3, RUNX3/CBFA3, RELM alpha, RXR alpha/NR2B1, RELM beta, RXR beta/NR2B2, RELT/TNFRSF19L, RXR gamma/NR2B3, Resistin, S100A10, SLITRK5, S100A8, SLP1, S100A9, SMAC/Diablo, S100B, Smad1, S100P, Smad2, SALL1, Smad3, delta-Sarcoglycan, Smad4, Sca-1/Ly6, Smad5, SCD-1, Smad7, SCF, Smad8, SCF R/c-kit, SMC1, SCGF, alpha-Smooth Muscle Actin, SCL/Tal1, SMUG1, SCP3/SYCP3, Snail, CXCL12/SDF-1, Sodium Calcium Exchanger 1, SDNSF/MCFD2, Soggy-1, alpha-Secretase, Sonic Hedgehog, gamma-Secretase, S or CSI, beta-Secretase, S or CS3, E-Selectin, Sortilin, L-Selectin, SOST, P-Selectin, SOX1, Semaphorin 3A, SOX2, Semaphorin 3C, SOX3, Semaphorin 3E, SOX7, Semaphorin 3F, SOX9, Semaphorin 6A, SOX10, Semaphorin 6B, SOX17, Semaphorin 6C, SOX21 Semaphorin 6D, SPARC, Semaphorin 7A, SPARC-like 1, Separase, SP-D, Serine/Threonine Phosphatase Substrate I, Spinesin, Serpin A1, F-Spondin, Serpin A3, SR-AI/MSR, Serpin A4/Kallistatin, Src, Serpin A5/Protein C Inhibitor, SREC-1/SR-F1, Serpin A8/Angiotensinogen, SREC-II, Serpin B5, SSEA-1, Serpin C1/Antithrombin-III, SSEA-3, Serpin D1/Heparin Cofactor II, SSEA-4, Serpin E1/PAI-1, ST7/LRP12, Serpin E2, Stabilin-1, Serpin F1, Stabilin-2, Serpin F2, Stanniocalcin 1, Serpin G1/C1 Inhibitor, Stanniocalcin 2, Serpin 12, STAT1, Serum Amyloid A1, STAT2, SF-1/NR5A1, STAT3, SGK, STAT4, SHBG, STAT5a/b, SHIP, STAT5a, SHP/NROB2, STAT5b, SHP-1, STAT6, SHP-2, VE-Statins, SIGIRR, Stella/Dppa3, Siglec-2/CD22, STRO-1, Siglec-3/CD33, Substance P, Siglec-5, Sulfamidase/SGSH, Siglec-6, Sulfatase Modifying Factor 1/SUMF1, Siglec-7, Sulfatase Modifying Factor 2/SUMF2, Siglec-9, SUMO1, Siglec-10, SUMO2/3/4, Siglec-11, SUMO3, Siglec-F, Superoxide Dismutase, SIGNR1/CD209, Superoxide Dismutase-1/Cu—Zn SOD, SIGNR4, Superoxide Dismutase-2/Mn-SOD, SIRP beta 1, Superoxide Dismutase-3/EC-SOD, SKI, Survivin, SLAM/CD150, Synapsin I, Sleeping Beauty Transposase, Syndecan-1/CD138, Slit3, Syndecan-2, SLITRK1, Syndecan-3, SLITRK2, Syndecan-4, SLITRK4, TACI/TNFRSF13B, TMEFF1/Tomoregulin-1, TAO2, TMEFF2, TAPP1, TNF-alpha/TNFSF1A, CCL17/TARC, TNF-beta/TNFSF1B, Tau, TNF RI/TNFRSF1A, TC21/R-Ras2, TNF RII/TNFRSF1B, TCAM-1, TOR, TCCR/WSX-1, TP-1, TC-PTP, TP63/TP73L, TDG, TR, CCL25/TECK, TR alpha/NR1A1, Tenascin C, TR beta 1/NR1A2, Tenascin R, TR2/NR2C1, TER-119, TR4NR2C2, TERT, TRA-1-85, Testican 1/SPOCK1, TRADD, Testican 2/SPOCK2, TRAF-1, Testican 3/SPOCK3, TRAF-2, TFPI, TRAF-3, TFPI-2, TRAF-4, TGF-alpha, TRAF-6, TGF-beta, TRAIL/TNFSF10, TGF-beta 1, TRAIL R1/TNFRSF10A, LAP (TGF-beta 1), TRAIL R2/TNFRSF10B, Latent TGF-beta 1, TRAIL R3/TNFRSF10C, TGF-beta 1.2, TRAIL R4/TNFRSF10D, TGF-beta 2, TRANCE/TNFSF11, TGF-beta 3, Tfr (Transferrin R), TGF-beta 5, Apo-Transferrin, Latent TGF-beta bp1, Holo-Transferrin, Latent TGF-beta bp2, Trappin-2/Elafin, Latent TGF-beta bp4, TREM-1, TGF-beta R/ALK-5, TREM-2, TGF-beta RII, TREM-3, TGF-beta RIIb, TREML1/TLT-1, TGF-beta RIII, TRF-1, Thermolysin, TRF-2, Thioredoxin-1, TRH-degrading Ectoenzyme/TRHDE, Thioredoxin-2, TRIM5, Thioredoxin-80, Tripeptidyl-Peptidase I, Thioredoxin-like 5/TRP14, TrkA, THOP1, TrkB, Thrombomodulin/CD141, TrkC, Thrombopoietin, TROP-2, Thrombopoietin R, Troponin I Peptide 3, Thrombospondin-1, Troponin T, Thrombospondin-2, TROY/TNFRSF19,

Thrombospondin-4, Trypsin 1, Thymopoietin, Trypsin 2/PRSS2, Thymus Chemokine-1, Trypsin 3/PRSS3, Tie-1, Tryptase-5/Prss32, Tie-2, Tryptase alpha/TPS1, TIM-1/KIM-1/HAVCR, Tryptasebeta-1/MCPT-7, TIM-2, Tryptase-beta-2/TPSB2, TIM-3, Tryptase epsilon/BSSP-4, TIM-4, Tryptase gamma-1/TPSG1, TIM-5, Tryptophan Hydroxylase, TIM-6, TSC22, TIMP-1, TSG, TIMP-2, TSG-6, TIMP-3, TSK, TIMP-4, TSLP, TL1A/TNFSF15, TSLP R, TLR1, TSP50, TLR2, beta-III Tubulin, TLR3, TWEAK/TNFSF12, TLR4, TWEAK R/TNFRSF12, TLR5, Tyk2, TLR6, Phospho-Tyrosine, TLR9, Tyrosine Hydroxylase, TLX/NR2E1, Tyrosine Phosphatase Substrate I, Ubiquitin, UNC5H3, Ugi, UNC5H4, UGRP1, UNG, ULBP-1, uPA, ULBP-2, uPAR, ULBP-3, URB, UNC5H1, UVDE, UNC5H2, Vanilloid R1, VEGF R, VASA, VEGF R1/Flt-1, Vasohibin, VEGF R2/KDR/Flk-1, Vasin, VEGF R3/Flt-4, Vasostatin, Versican, Vav-1, VG5Q, VCAM-1, VHR, VDR/NR1H3, Vimentin, VEGF, Vitronectin, VEGF-B, VLDLR, VEGF-C, vWF-A2, VEGF-D, Synuclein-alpha, Ku70, WASP, Wnt-7b, WIF-1, Wnt-8a WISP-1/CCN4, Wnt-8b, WNK1, Wnt-9a, Wnt-1, Wnt-9b, Wnt-3a, Wnt-10a, Wnt-4, Wnt-10b, Wnt-5a, Wnt-11, Wnt-5b, wntNS3, Wnt7a, XCR1, XPE/DDBI, XEDAR, XPE/DDB2, Xg, XPF, XIAP, XPG, XPA, XPV, XPD, XRCC1, Yes, YY1, EphA4.

[0230] Numerous human ion channels are targets of particular interest. Non-limiting examples include 5-hydroxytryptamine 3 receptor B subunit, 5-hydroxytryptamine 3 receptor precursor, 5-hydroxytryptamine receptor 3 subunit C, AAD14 protein, Acetylcholine receptor protein, alpha subunit precursor, Acetylcholine receptor protein, beta subunit precursor, Acetylcholine receptor protein, delta subunit precursor, Acetylcholine receptor protein, epsilon subunit precursor, Acetylcholine receptor protein, gamma subunit precursor, Acid sensing ion channel 3 splice variant b, Acid sensing ion channel 3 splice variant c, Acid sensing ion channel 4, ADP-ribose pyrophosphatase, mitochondrial precursor, Alpha1A-voltage-dependent calcium channel, Amiloride-sensitive cation channel 1, neuronal, Amiloride-sensitive cation channel 2, neuronal Amiloride-sensitive cation channel 4, isoform 2, Amiloride-sensitive sodium channel, Amiloride-sensitive sodium channel alpha-subunit, Amiloride-sensitive sodium channel beta-subunit, Amiloride-sensitive sodium channel delta-subunit, Amiloride-sensitive sodium channel gamma-subunit, Annexin A7, Apical-like protein, ATP-sensitive inward rectifier potassium channel 1, ATP-sensitive inward rectifier potassium channel 10, ATP-sensitive inward rectifier potassium channel 11, ATP-sensitive inward rectifier potassium channel 14, ATP-sensitive inward rectifier potassium channel 15, ATP-sensitive inward rectifier potassium channel 8, Calcium channel alpha12.2 subunit, Calcium channel alpha12.2 subunit, Calcium channel alpha1E subunit, delta19 delta40 delta46 splice variant, Calcium-activated potassium channel alpha subunit 1, Calcium-activated potassium channel beta subunit 1, Calcium-activated potassium channel beta subunit 2, Calcium-activated potassium channel beta subunit 3, Calcium-dependent chloride channel-1, Cation channel TRPM4B, CDNA FLJ90453 fis, clone NT2RP3001542, highly similar to Potassium channel tetramerisation domain containing 6, CDNA FLJ90663 fis, clone PLACE1005031, highly similar to Chloride intracellular channel protein 5, CGMP-gated cation channel beta subunit, Chloride channel protein, Chloride channel protein 2, Chloride channel protein 3, Chloride channel protein 4, Chloride channel protein 5, Chloride channel protein 6, Chloride

channel protein CIC-Ka, Chloride channel protein CIC-Kb, Chloride channel protein, skeletal muscle, Chloride intracellular channel 6, Chloride intracellular channel protein 3, Chloride intracellular channel protein 4, Chloride intracellular channel protein 5, CHRNA3 protein, Clcn3e protein, CLCNKB protein, CNGA4 protein, Cullin-5, Cyclic GMP gated potassium channel, Cyclic-nucleotide-gated cation channel 4, Cyclic-nucleotide-gated cation channel alpha 3, Cyclic-nucleotide-gated cation channel beta 3, Cyclic-nucleotide-gated olfactory channel, Cystic fibrosis transmembrane conductance regulator, Cytochrome B-245 heavy chain, Dihydropyridine-sensitive L-type, calcium channel alpha-2/delta subunits precursor, FXYD domain-containing ion transport regulator 3 precursor, FXYD domain-containing ion transport regulator 5 precursor, FXYD domain-containing ion transport regulator 6 precursor, FXYD domain-containing ion transport regulator 7, FXYD domain-containing ion transport regulator 8 precursor, G protein-activated inward rectifier potassium channel 1, G protein-activated inward rectifier potassium channel 2, G protein-activated inward rectifier potassium channel 3, G protein-activated inward rectifier potassium channel 4, Gamma-aminobutyric-acid receptor alpha-1 subunit precursor, Gamma-aminobutyric-acid receptor alpha-2 subunit precursor, Gamma-aminobutyric-acid receptor alpha-3 subunit precursor, Gamma-aminobutyric-acid receptor alpha-4 subunit precursor, Gamma-aminobutyric-acid receptor alpha-5 subunit precursor, Gamma-aminobutyric-acid receptor alpha-6 subunit precursor, Gamma-aminobutyric-acid receptor beta-1 subunit precursor, Gamma-aminobutyric-acid receptor beta-2 subunit precursor, Gamma-aminobutyric-acid receptor beta-3 subunit precursor, Gamma-aminobutyric-acid receptor delta subunit precursor, Gamma-aminobutyric-acid receptor epsilon subunit precursor, Gamma-aminobutyric-acid receptor gamma-1 subunit precursor, Gamma-aminobutyric-acid receptor gamma-3 subunit precursor, Gamma-aminobutyric-acid receptor pi subunit precursor, Gamma-aminobutyric-acid receptor rho-1 subunit precursor, Gamma-aminobutyric-acid receptor rho-2 subunit precursor, Gamma-aminobutyric-acid receptor theta subunit precursor, GluR6 kainate receptor, Glutamate receptor 1 precursor, Glutamate receptor 2 precursor, Glutamate receptor 3 precursor, Glutamate receptor 4 precursor, Glutamate receptor 7, Glutamate receptor B, Glutamate receptor delta-1 subunit precursor, Glutamate receptor, ionotropic kainate 1 precursor, Glutamate receptor, ionotropic kainate 2 precursor, Glutamate receptor, ionotropic kainate 3 precursor, Glutamate receptor, ionotropic kainate 4 precursor, Glutamate receptor, ionotropic kainate 5 precursor, Glutamate [NMDA] receptor subunit 3A precursor, Glutamate [NMDA] receptor subunit 3B precursor, Glutamate [NMDA] receptor subunit epsilon 1 precursor, Glutamate [NMDA] receptor subunit epsilon 2 precursor, Glutamate [NMDA] receptor subunit epsilon 4 precursor, Glutamate [NMDA] receptor subunit zeta 1 precursor, Glycine receptor alpha-1 chain precursor, Glycine receptor alpha-2 chain precursor, Glycine receptor alpha-3 chain precursor, Glycine receptor beta chain precursor, H/ACA ribonucleoprotein complex subunit 1, High affinity immunoglobulin epsilon receptor beta-subunit, Hypothetical protein DKFZp31310334, Hypothetical protein DKFZp761M1724, Hypothetical protein FLJ12242, Hypothetical protein FLJ14389, Hypothetical protein FLJ14798, Hypothetical protein FLJ14995, Hypothetical protein FLJ16180, Hypothetical protein FLJ16802, Hypothetical protein FLJ32069,

Hypothetical protein FLJ37401, Hypothetical protein FLJ38750, Hypothetical protein FLJ40162, Hypothetical protein FLJ41415, Hypothetical protein FLJ90576, Hypothetical protein FLJ90590, Hypothetical protein FLJ90622, Hypothetical protein KCTD15, Hypothetical protein MGC15619, Inositol 1,4,5-trisphosphate receptor type 1, Inositol 1,4,5-trisphosphate receptor type 2, Inositol 1,4,5-trisphosphate receptor type 3, Intermediate conductance calcium-activated potassium channel protein 4, Inward rectifier potassium channel 13, Inward rectifier potassium channel 16, Inward rectifier potassium channel 4, Inward rectifying K(+) channel negative regulator Kir2.2v, Kainate receptor subunit KA2a, KCNH5 protein, KCTD17 protein, KCTD2 protein, Keratinocytes associated transmembrane protein 1, Kv channel-interacting protein 4, Melastatin 1, Membrane protein MLC1, MGC15619 protein, Mucolipin-1, Mucolipin-2, Mucolipin-3, Multidrug resistance-associated protein 4, N-methyl-D-aspartate receptor 2C subunit precursor, NADPH oxidase homolog 1, Nav1.5, Neuronal acetylcholine receptor protein, alpha-10 subunit precursor, Neuronal acetylcholine receptor protein, alpha-2 subunit precursor, Neuronal acetylcholine receptor protein, alpha-3 subunit precursor, Neuronal acetylcholine receptor protein, alpha-4 subunit precursor, Neuronal acetylcholine receptor protein, alpha-5 subunit precursor, Neuronal acetylcholine receptor protein, alpha-6 subunit precursor, Neuronal acetylcholine receptor protein, alpha-7 subunit precursor, Neuronal acetylcholine receptor protein, alpha-9 subunit precursor, Neuronal acetylcholine receptor protein, beta-2 subunit precursor, Neuronal acetylcholine receptor protein, beta-3 subunit precursor, Neuronal acetylcholine receptor protein, beta-4 subunit precursor, Neuronal voltage-dependent calcium channel alpha 2D subunit, P2X purinoceptor 1, P2X purinoceptor 2, P2X purinoceptor 3, P2X purinoceptor 4, P2X purinoceptor 5, P2X purinoceptor 6, P2X purinoceptor 7, Pancreatic potassium channel TALK-1b, Pancreatic potassium channel TALK-1c, Pancreatic potassium channel TALK-1d, Phospholemman precursor, Plasmolipin, Polycystic kidney disease 2 related protein, Polycystic kidney disease 2-like 1 protein, Polycystic kidney disease 2-like 2 protein, Polycystic kidney disease and receptor for egg jelly related protein precursor, Polycystin-2, Potassium channel regulator, Potassium channel subfamily K member 1, Potassium channel subfamily K member 10, Potassium channel subfamily K member 12, Potassium channel subfamily K member 13, Potassium channel subfamily K member 15, Potassium channel subfamily K member 16, Potassium channel subfamily K member 17, Potassium channel subfamily K member 2, Potassium channel subfamily K member 3, Potassium channel subfamily K member 4, Potassium channel subfamily K member 5, Potassium channel subfamily K member 6, Potassium channel subfamily K member 7, Potassium channel subfamily K member 9, Potassium channel tetramerisation domain containing 3, Potassium channel tetramerisation domain containing protein 12, Potassium channel tetramerisation domain containing protein 14, Potassium channel tetramerisation domain containing protein 2, Potassium channel tetramerisation domain containing protein 4, Potassium channel tetramerisation domain containing protein 5, Potassium channel tetramerization domain containing 10, Potassium channel tetramerization domain containing protein 13, Potassium channel tetramerization domain-containing 1, Potassium voltage-gated channel subfamily A member 1, Potassium voltage-gated channel subfamily A member 2, Potassium voltage-

gated channel subfamily A member 4, Potassium voltage-gated channel subfamily A member 5, Potassium voltage-gated channel subfamily A member 6, Potassium voltage-gated channel subfamily B member 1, Potassium voltage-gated channel subfamily B member 2, Potassium voltage-gated channel subfamily C member 1, Potassium voltage-gated channel subfamily C member 3, Potassium voltage-gated channel subfamily C member 4, Potassium voltage-gated channel subfamily D member 1, Potassium voltage-gated channel subfamily D member 2, Potassium voltage-gated channel subfamily D member 3, Potassium voltage-gated channel subfamily E member 1, Potassium voltage-gated channel subfamily E member 2, Potassium voltage-gated channel subfamily E member 3, Potassium voltage-gated channel subfamily E member 4, Potassium voltage-gated channel subfamily F member 1, Potassium voltage-gated channel subfamily E member 1, Potassium voltage-gated channel subfamily G member 2, Potassium voltage-gated channel subfamily G member 3, Potassium voltage-gated channel subfamily G member 4, Potassium voltage-gated channel subfamily H member 1, Potassium voltage-gated channel subfamily H member 2, Potassium voltage-gated channel subfamily H member 3, Potassium voltage-gated channel subfamily H member 4, Potassium voltage-gated channel subfamily H member 5, Potassium voltage-gated channel subfamily H member 6, Potassium voltage-gated channel subfamily H member 7, Potassium voltage-gated channel subfamily H member 8, Potassium voltage-gated channel subfamily KQT member 1, Potassium voltage-gated channel subfamily KQT member 2, Potassium voltage-gated channel subfamily KQT member 3, Potassium voltage-gated channel subfamily KQT member 4, Potassium voltage-gated channel subfamily KQT member 5, Potassium voltage-gated channel subfamily S member 1, Potassium voltage-gated channel subfamily S member 2, Potassium voltage-gated channel subfamily S member 3, Potassium voltage-gated channel subfamily V member 2, Potassium voltage-gated channel, subfamily H, member 7, isoform 2, Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1, Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 2, Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 3, Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4, Probable mitochondrial import receptor subunit TOM40 homolog, Purinergic receptor P2X5, isoform A, Putative 4 repeat voltage-gated ion channel, Putative chloride channel protein 7, Putative GluR6 kainate receptor, Putative ion channel protein CATSPER2 variant 1, Putative ion channel protein CATSPER2 variant 2, Putative ion channel protein CATSPER2 variant 3, Putative regulator of potassium channels protein variant 1, Putative tyrosine-protein phosphatase TPTE, Ryanodine receptor 1, Ryanodine receptor 2, Ryanodine receptor 3, SH3 KBP1 binding protein 1, Short transient receptor potential channel 1, Short transient receptor potential channel 4, Short transient receptor potential channel 5, Short transient receptor potential channel 6, Short transient receptor potential channel 7, Small conductance calcium-activated potassium channel protein 1, Small conductance calcium-activated potassium channel protein 2, isoform b, Small conductance calcium-activated potassium channel protein 3, isoform b, Small-conductance calcium-activated potassium channel SK2, Small-conductance calcium-activated potassium channel SK3, Sodium channel, Sodium channel beta-1 subunit precursor, Sodium channel

protein type II alpha subunit, Sodium channel protein type III alpha subunit, Sodium channel protein type IV alpha subunit, Sodium channel protein type IX alpha subunit, Sodium channel protein type V alpha subunit, Sodium channel protein type VII alpha subunit, Sodium channel protein type VIII alpha subunit, Sodium channel protein type X alpha subunit, Sodium channel protein type XI alpha subunit, Sodium- and chloride-activated ATP-sensitive potassium channel, Sodium/potassium-transporting ATPase gamma chain, Sperm-associated cation channel 1, Sperm-associated cation channel 2, isoform 4, Syntaxin-1B1, Transient receptor potential cation channel subfamily A member 1, Transient receptor potential cation channel subfamily M member 2, Transient receptor potential cation channel subfamily M member 3, Transient receptor potential cation channel subfamily M member 6, Transient receptor potential cation channel subfamily M member 7, Transient receptor potential cation channel subfamily V member 1, Transient receptor potential cation channel subfamily V member 2, Transient receptor potential cation channel subfamily V member 3, Transient receptor potential cation channel subfamily V member 4, Transient receptor potential cation channel subfamily V member 5, Transient receptor potential cation channel subfamily V member 6, Transient receptor potential channel 4 epsilon splice variant, Transient receptor potential channel 4 zeta splice variant, Transient receptor potential channel 7 gamma splice variant, Tumor necrosis factor, alpha-induced protein 1, endothelial, Two-pore calcium channel protein 2, VDAC4 protein, Voltage gated potassium channel Kv3.2b, Voltage gated sodium channel beta 1B subunit, Voltage-dependent anion channel, Voltage-dependent anion channel 2, Voltage-dependent anion-selective channel protein 1, Voltage-dependent anion-selective channel protein 2, Voltage-dependent anion-selective channel protein 3, Voltage-dependent calcium channel gamma-1 subunit, Voltage-dependent calcium channel gamma-2 subunit, Voltage-dependent calcium channel gamma-3 subunit, Voltage-dependent calcium channel gamma-4 subunit, Voltage-dependent calcium channel gamma-5 subunit, Voltage-dependent calcium channel gamma-6 subunit, Voltage-dependent calcium channel gamma-7 subunit, Voltage-dependent calcium channel gamma-8 subunit, Voltage-dependent L-type calcium channel alpha-1C subunit, Voltage-dependent L-type calcium channel alpha-1D subunit, Voltage-dependent L-type calcium channel alpha-1S subunit, Voltage-dependent L-type calcium channel beta-1 subunit, Voltage-dependent L-type calcium channel beta-2 subunit, Voltage-dependent L-type calcium channel beta-3 subunit, Voltage-dependent L-type calcium channel beta-4 subunit, Voltage-dependent N-type calcium channel alpha-1B subunit, Voltage-dependent P/Q-type calcium channel alpha-1A subunit, Voltage-dependent R-type calcium channel alpha-1E subunit, Voltage-dependent T-type calcium channel alpha-1G subunit, Voltage-dependent T-type calcium channel alpha-1H subunit, Voltage-dependent T-type calcium channel alpha-1I subunit, Voltage-gated L-type calcium channel alpha-1 subunit, Voltage-gated potassium channel beta-1 subunit, Voltage-gated potassium channel beta-2 subunit, Voltage-gated potassium channel beta-3 subunit, Voltage-gated potassium channel KCNA7.

[0231] Exemplary GPCRs include but are not limited to Class A Rhodopsin like receptors such as Musc. acetylcholine Vertebrate type 1, Musc. acetylcholine Vertebrate type 2, Musc. acetylcholine Vertebrate type 3, Musc. acetylcholine

Vertebrate type 4; Adrenoceptors (Alpha Adrenoceptors type 1, Alpha Adrenoceptors type 2, Beta Adrenoceptors type 1, Beta Adrenoceptors type 2, Beta Adrenoceptors type 3, Dopamine Vertebrate type 1, Dopamine Vertebrate type 2, Dopamine Vertebrate type 3, Dopamine Vertebrate type 4, Histamine type 1, Histamine type 2, Histamine type 3, Histamine type 4, Serotonin type 1, Serotonin type 2, Serotonin type 3, Serotonin type 4, Serotonin type 5, Serotonin type 6, Serotonin type 7, Serotonin type 8, other Serotonin types, Trace amine, Angiotensin type 1, Angiotensin type 2, Bombesin, Bradykinin, C5a anaphylatoxin, Finet-leu-phe, APJ like, Interleukin-8 type A, Interleukin-8 type B, Interleukin-8 type others, C—C Chemokine type 1 through type 11 and other types, C—X—C Chemokine (types 2 through 6 and others), C—X3-C Chemokine, Cholecystokinin CCK, CCK type A, CCK type B, CCK others, Endothelin, Melanocortin (Melanocyte stimulating hormone, Adrenocorticotrophic hormone, Melanocortin hormone), Duffy antigen, Prolactin-releasing peptide (GPR10), Neuropeptide Y (type 1 through 7), Neuropeptide Y, Neuropeptide Y other, Neurotensin, Opioid (type D, K, M, X), Somatostatin (type 1 through 5), Tachykinin (Substance P (NK1), Substance K (NK2), Neuromedin K (NK3), Tachykinin like 1, Tachykinin like 2, Vasopressin/vasotocin (type 1 through 2), Vasotocin, Oxytocin/mesotocin, Conopressin, Galanin like, Proteinase-activated like, Orexin & neuropeptides FF, QRFP, Chemokine receptor-like, Neuromedin U like (Neuromedin U, PRXamide), hormone protein (Follicle stimulating hormone, Lutropin-choriogonadotropic hormone, Thyrotropin, Gonadotropin type I, Gonadotropin type II), (Rhodopsin, Rhodopsin Vertebrate (types 1-5), Rhodopsin Vertebrate type 5, Rhodopsin Arthropod, Rhodopsin Arthropod type 1, Rhodopsin Arthropod type 2, Rhodopsin Arthropod type 3, Rhodopsin Mollusc, Rhodopsin, Olfactory (Olfactory II fam 1 through 13), Prostaglandin (prostaglandin E2 subtype EP1, Prostaglandin E2/D2 subtype EP2, prostaglandin E2 subtype EP3, Prostaglandin E2 subtype EP4, Prostaglandin F2-alpha, Prostacyclin, Thromboxane, Adenosine type 1 through 3, Purinoceptors, Purinoceptor P2RY1-4,6,11 GPR91, Purinoceptor P2RY5,8,9,10 GPR35,92,174, Purinoceptor P2RY12-14 GPR87 (UDP-Glucose), Cannabinoid, Platelet activating factor, Gonadotropin-releasing hormone, Gonadotropin-releasing hormone type I, Gonadotropin-releasing hormone type II, Adipokinetic hormone like, Corazonin, Thyrotropin-releasing hormone & Secretagogue, Thyrotropin-releasing hormone, Growth hormone secretagogue, Growth hormone secretagogue like, Ecdysis-triggering hormone (ETHR), Melatonin, Lysosphingolipid & LPA (EDG), Sphingosine 1-phosphate Edg-1, Lysophosphatidic acid Edg-2, Sphingosine 1-phosphate Edg-3, Lysophosphatidic acid Edg-4, Sphingosine 1-phosphate Edg-5, Sphingosine 1-phosphate Edg-6, Lysophosphatidic acid Edg-7, Sphingosine 1-phosphate Edg-8, Edg Other Leukotriene B4 receptor, Leukotriene B4 receptor BLT1, Leukotriene B4 receptor BLT2, Class A Orphan/other, Putative neurotransmitters, SREB, Mas proto-oncogene & Mas-related (MRGs), GPR45 like, Cysteinyl leukotriene, G-protein coupled bile acid receptor, Free fatty acid receptor (GP40, GP41, GP43), Class B Secretin like, Calcitonin, Corticotropin releasing factor, Gastric inhibitory peptide, Glucagon, Growth hormone-releasing hormone, Parathyroid hormone, PACAP, Secretin, Vasoactive intestinal polypeptide, Latrophilin, Latrophilin type 1, Latrophilin type 2, Latrophilin type 3, ETL receptors, Brain-specific angiogenesis inhibitor (BAI), Methuselah-like proteins

(MTH), Cadherin EGF LAG (CELSR), Very large G-protein coupled receptor, Class C Metabotropic glutamate/pheromone, Metabotropic glutamate group I through III, Calcium-sensing like, Extracellular calcium-sensing, Pheromone, calcium-sensing like other, Putative pheromone receptors, GABA-B, GABA-B subtype 1, GABA-B subtype 2, GABA-B like, Orphan GPCR5, Orphan GPCR6, Bride of sevenless proteins (BOSS), Taste receptors (TIR), Class D Fungal pheromone, Fungal pheromone A-Factor like (STE2, STE3), Fungal pheromone B like (BAR, BBR, RCB, PRA), Class E cAMP receptors, Ocular albinism proteins, Frizzled/Smoothed family, frizzled Group A (Fz 1&2&4&5&7-9), frizzled Group B (Fz 3 & 6), frizzled Group C (other), Vomeronasal receptors, Nematode chemoreceptors, Insect odorant receptors, and Class Z Archaeal/bacterial/fungal opsins.

[0232] The subject MURPs can be designed to target any cellular proteins including but not limited to cell surface protein, secreted protein, cytosolic protein, and nuclear protein. A target of particular interest is an ion channel.

[0233] Ion channels constitute a superfamily of proteins, including the family of potassium channels (K-channels), the family of sodium channels (Na-channels), the family of calcium channels (Ca-channels), the family of Chlorine channels (Cl-channels) and the family of acetylcholine channels. Each of these families contains subfamilies and each subfamily typically contains specific channels derived from single genes. For example, the K-channel family contains subfamilies of voltage-gated K-channels called Kv1.x and Kv3.x. The subfamily Kv1.x contains the channels Kv1.1, Kv1.2 and Kv1.3, which correspond to the products of single genes and are thus called 'species'. The classification applies to the Na-, Ca-, Cl- and other families of channels as well.

[0234] Ion channels can also be classified according to the mechanisms by which the channels are operated. Specifically, the main types of ion channel proteins are characterized by the method employed to open or close the channel protein to either permit or prevent specific ions from permeating the channel protein and crossing a lipid bilayer cellular membrane. One important type of channel protein is the voltage-gated channel protein, which is opened or closed (gated) in response to changes in electrical potential across the cell membrane. The voltage-gated sodium channel 1.6 (Nav1.6) is of particular interest as a therapeutic target. Another type of ion channel protein is the mechanically gated channel, for which a mechanical stress on the protein opens or closes the channel. Still another type is called a ligand-gated channel, which opens or closes depending on whether a particular ligand is bound to the protein. The ligand can be either an extracellular moiety, such as a neurotransmitter, or an intracellular moiety, such as an ion or nucleotide.

[0235] Ion channels generally permit passive flow of ions down an electrochemical gradient, whereas ion pumps use ATP to transport against a gradient. Coupled transporters, both antiporters and symporters, allow movement of one ion species against its gradient, powered by the downhill movement of another ion species.

[0236] One of the most common types of channel proteins, found in the membrane of almost all animal cells, permits the specific permeation of potassium ions across a cell membrane. In particular, potassium ions permeate rapidly across cell membranes through K⁺ channel proteins (up to 10⁻⁸ ions per second). Moreover, potassium channel proteins have the ability to distinguish among potassium ions, and other small alkali metal ions, such as Li⁺ or Na⁺ with great fidelity. In

particular, potassium ions are at least ten thousand times more permanent than sodium ions. Potassium channel proteins typically comprise four (usually identical) subunits, so their cell surface targets are present as tetramers, allowing tetravalent binding of MURPs. One type of subunit contains six long hydrophobic segments (which can be membrane-spanning), while the other types contains two hydrophobic segments.

[0237] Another significant family of channels is calcium channel. Calcium channels are generally classified according to their electrophysiological properties as Low-voltage-activated (LVA) or High-voltage-activated (HVA) channels. HVA channels comprises at least three groups of channels, known as L-, N- and P/Q-type channels. These channels have been distinguished one from another electrophysiologically as well as bio-chemically on the basis of their pharmacology and ligand binding properties. For instance, dihydropyridines, diphenyl-alkylamines and piperidines bind to the α_1 subunit of the L-type calcium channel and block a proportion of HVA calcium currents in neuronal tissue, which are termed L-type calcium currents. N-type calcium channels are sensitive to omega conopeptides, but are relatively insensitive to dihydropyridine compounds, such as nimodipine and nifedipine. P/Q-type channels, on the other hand, are insensitive to dihydropyridines, but are sensitive to the funnel web spider toxin Aga IIIA. R-type calcium channels, like L-, N-, P- and Q-type channels, are activated by large membrane depolarizations, and are thus classified as high voltage-activated (HVA) channels. R-type channels are generally insensitive to dihydropyridines and omega conopeptides, but, like P/Q, L and N channels, are sensitive to the funnel web spider toxin Aga IVa. Immunocytochemical staining studies indicate that these channels are located throughout the brain, particularly in deep midline structures (caudate-putamen, thalamus, hypothalamus, amygdala, cerebellum) and in the nuclei of the ventral midbrain and brainstem. Neuronal voltage-sensitive calcium channels typically consists of a central α_1 subunit, an α_2/δ subunit, a β subunit and a 95 kD subunit.

[0238] Additional non-limiting examples include Kir (an inwardly rectified potassium channel), Kv (a voltage-gated potassium channel), Nav (a voltage-gated sodium channel), Cav (a voltage-gated calcium channel), CNG (cyclic nucleotide-gated channel), HCN (hyperpolarization-activated channel), TRP (a transient receptor potential channel), CIC (a chloride channel), CFTR (a cystic fibrosis transmembrane conductance regulator, a chloride channel), IP3R (a inositol trisphosphate receptor), RYR (a ryanodine receptor). Other channel types are 2-pore channels, glutamate-receptors (AMPA, NMDA, KA), M2, Connexins and Cys-loop receptors.

[0239] A common layout for ion channel proteins, such as Kv1.2, Kv3.1, Shaker, TRPC1 and TRPC5 is to have six membrane-spanning segments, arranged as follows:

[0240] N-terminus---S1---E1---S2---X1---S3---E2---S4---X2---S5---E3---S6---C-terminus

[0241] Wherein S1-6 are membrane-spanning sequences, E1-3 are extracellular surface loops and X1-2 are intracellular surface loops. The E3 loop is generally the longest of the three extracellular loops and is hydrophilic so it is a good target for drugs and MURPs to bind. The pore-forming part of most channels is a multimeric (e.g. tetrameric or rarely pentameric) complex of membrane-spanning alpha-helices. There is generally a pore loop, which is a region of the protein that loops back into the membrane to form the selectivity filter that

determines which ion species can permeate. Such channels are called 'pore-loop' channels.

[0242] The ion channels are valuable targets for drug design because they are involved in a broad range of physiological processes. In human, there exist approximately over three hundreds of ion channel proteins, many of which have been implicated in genetic diseases. For example, aberrant expression or function of ion channels has been shown to cause a wide arrange of diseases including cardiac, neuronal, muscular, respiratory metabolic diseases. This section focuses on ion channels, but the same concepts and approaches are equally applicable to all membrane proteins, including 7TMs, 1TMs, G-proteins and G-Protein Coupled receptors (GPCRs), etc. Some of the ion channels are GPCRs.

[0243] Ion channels typically form large macromolecular complexes that include tightly bound accessory protein subunits and combinatorial use of such subunits contributes to the diversity of ion channels. These accessory proteins can also be the binding targets of the subject MURPs, microproteins and toxins.

[0244] The subject MURPs can be designed to bind any of the channels known in the art and to those specifically exemplified herein. MURPs exhibiting a desired ion channel binding capability (encompassing specificity and avidity) can be selected by any recombinant and biochemical (e.g. expression and display) techniques known in the art. For instance, MURPs can be displayed by a genetic package including but not limited to phages and spores, and be subjected to panning against intact cell membranes, or preferably intact cells such as whole mammalian cells. To remove the phage that bind to the other, non-target cell surface molecules, the standard approach was to perform subtraction panning against similar cell lines that had a low or non-detectable level of the target receptor. However, Popkov et al. (J. Immunol. Methods 291: 137-151 (2004)) showed that related cell types are not ideal for subtraction because they generally have a reduced but still significant level of the target on their surface, which reduces the number of desired phage clones. This problem occurs even when panning on cells that have been transfected with the gene encoding the target, followed by negative selection/subtraction on the same cell-line which was not transfected, especially when the native target gene was not knocked out. Instead, Popkov et al. showed that the negative selection or subtraction panning works much better if performed with an excess of the same cells that are used for normal panning (positive selection), except that the target has now been blocked with a high-affinity, target-specific inhibitor, such as a small molecule, peptide or an antibody to the target, which makes the active site unavailable. This process is called "negative selection with epitope-masked cells", which is particularly useful in selecting the subject MURPs with a desired ion-channel binding capability.

[0245] In a separate embodiment, the present invention provides microproteins, and particularly microproteins exhibiting binding capability towards at least one family of ion channels. The present invention also provides a genetic package displaying such microproteins. Non-limiting ion-channel examples to which the subject microproteins bind are sodium, potassium, calcium, acetylcholine, and chlorine channels. Of particular interest are those microproteins and the genetic packages displaying such microproteins, which exhibit binding capability towards native targets. Native targets are generally natural molecules or fragments, derivatives

thereof that the microprotein is known to bind, typically including those known binding targets that have been reported in the literature.

[0246] The subject invention also provides a genetic package displaying an ion-channel-binding microprotein which has been modified. The modified microprotein may (a) binds to a different family of channel as compared to the corresponding unmodified microprotein; (b) binds to a different subfamily of the same channel family as compared to the corresponding unmodified microprotein; (c) binds to a different species of the same subfamily of channel as compared to the corresponding unmodified microprotein; (d) the microprotein binds to a different site on the same channel as compared to the corresponding unmodified microprotein; and/or (e) binds to the same site of the same channel but yield a different biological effect as compared to the corresponding unmodified microprotein.

[0247] FIGS. 22 and 46 show how microprotein domains or toxins that each bind at different sites of the same ion channel can be combined into a single protein. The two binding sites that these two microproteins bind to can be on two channels from different families, two channels from the same family but a different subfamily, two channels from the same subfamily but a different species (gene product), or two different binding sites on the same channel (species) or they can (simultaneously or not) bind the same binding site on the same channel (species) since the channels are multimeric. The binding modules and domains that bind to sites on the channels can be microprotein domains (natural or non-natural, 2- to 8-disulfide containing), one-disulfide peptides, or linear peptides. These modules can be selected independently and combined, or one can be selected from a library to bind in the presence of one fixed, active binding module. In the latter case, the display library would display multiple modules of which one would contain a library of variants. A typical goal is to select a dimer from this library that has a higher affinity than the active monomer that was the starting point.

[0248] In another embodiment, the present invention provides a protein comprising a plurality of ion-channel binding domains, wherein individual domains are microprotein domains that have been modified such that (a) the microprotein domains bind to a different family of channel as compared to the corresponding unmodified microprotein domains; (b) the microprotein domains bind to a different subfamily of the same channel family as compared to the corresponding unmodified microprotein domains; (c) the microprotein domains bind to a different species of the same subfamily as compared to the corresponding unmodified microprotein domains; (d) the microprotein domains bind to a different site on the same channel as compared to the corresponding unmodified microprotein domains; (e) the microprotein domains bind to the same site of the same channel but yield a different biological effect as compared to the corresponding unmodified microprotein domains; and/or (f) the microprotein domains bind to the same site of the same channel and yield the same biological effect as compared to the corresponding unmodified microprotein domains. Where desired, the microprotein domains may comprise natural or non-natural sequences. The individual domains can be linked together via a heterologous linker. The individual microprotein domains can bind to the same or different channel family, same or different channel subfamily, same or different species of the same subfamily, same or different site on the same channel.

[0249] The subject microproteins can be a toxin. Preferably, the toxin retains in part or in whole its toxicity spectrum. In particular, venomous animals, such as snakes, encounter a range of prey and intruder species and the venom toxins differ in activity for the different receptors of the different species. The venom consists of a large number of related and unrelated toxins, with each toxin having a "spectrum of activity", which can be defined as all of the receptors from all of the species on which that toxin has measurable activity. All of the targets in the 'spectrum of activity' are considered "native targets" and this includes any human targets that the toxin is active against. The native target(s) of a microprotein or toxin include all of the targets that the toxin is reported to inhibit in the literature. The higher the affinity or activity on a target, the more likely that target is the natural, native target, but it is not uncommon for toxins to act on multiple targets within the same species. Native target(s) can be human or non-human receptors that the toxin is active against.

[0250] For the toxin to retain the ability to bind to cells after fusion to the display vector, it may be desirable to test both the N-terminus and C-terminus for fusion and to test a variety of fusion sites (i.e., 0, 1, 2, 3, 4, 5, 6 amino acids before the first cysteine or after the last cysteine of the toxin domain, if the toxin domain is a cysteine-containing domain) using a synthetic DNA library approach, preferably encoding a library of glycine-rich linkers, which form the smallest amino acid chain, are uncharged and are most likely to be compatible with binding of the toxin to the target. Since the N-terminal amino group and the C-terminal carboxyl groups may be involved in target binding, the library should contain a lysine or an arginine to mimic the positively charged amino group (or fusions to the N-terminus of the toxin) and a glutamate or an aspartate to mimic the negatively charged carboxyl group (for fusions to the C-terminus of the toxin).

[0251] The inhibitor(s) that are used to block the target during negative selection can be small molecules, peptides or proteins, and natural or non-natural. In addition to simple subtraction, the choice of the mixture of inhibitors is a valuable tool to control the specificity of the ion channel inhibitors that are being designed. Because there are over three hundreds ion channels in total, with partially overlapping specificities and sequence similarities, and multiple modulatory sites per channel, each having a different effect, the specificity requirement can be complex.

[0252] When modifying the activity of a toxin, or when combining two different toxins into a single protein, the two toxins can bind the same channel at the same site and have the same physiologic effect, or the two toxins can bind the same channel at the same site and have a different physiologic effect, or the two toxins can bind to the same channel at a different site, or the two toxins can bind to different channels that belong to the same subfamily (i.e. Kv1.3 and Kv1.2; meaning product of a different gene or 'species'), or the two toxins can bind to different channels that belong to the same family (i.e. both are K-channels), or the two toxins can bind to channels that belong to different families (i.e. K-channels versus Na-channels).

[0253] Ion channels typically have many transmembrane segments (24 for sodium channels) and thus offer a number of different, non-competing and non-overlapping binding sites for modulators to alter the activity of the channel in different ways. One approach is to create binders for one site on the same ion channel from existing binders for a different site, even if these sites are unrelated. To achieve this, the existing

toxin can be used as a targeting agent for a library of 1-, 2-, 3-, or 4-disulfide proteins that is separated from the targeting toxin by a flexible linker of 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40 or 50 amino acids. It is useful if the affinity of the targeting agent is not too high, so that the affinity of the new library can have a significant contribution to the overall affinity. Another approach is to create new modulators for channels from existing modulators for other channels that are related in sequence or in structure. The conotoxin family, for example, contains sequence-related and structure-related modulators for Ca-, K, Na-channels and nicotinic acetylcholine receptors. It appears feasible to convert a K-channel modulator into a Na-channel modulator using a library of conotoxin-derivatives, or vice versa. For example, Kappa-conotoxins inhibit K-channels, Mu-conotoxins and Delta-conotoxins inhibit Na-channels, Omega-conotoxins inhibit Ca-channels and Alpha-conotoxins inhibit acetylcholine receptors.

[0254] The proximity of different binding sites, each with a different effect on channel activity, from the same ion channel makes it attractive to link the inhibitors using flexible linkers, creating a single inhibitor with two domains, each binding at a different site. Or a single protein with two domains that bind at different copies of the same site, yielding a bivalent, high affinity interaction (avidity). This approach has not been taken by natural toxins, presumably because they must act fast and thus stay small in order to have maximal tissue penetration, but for pharmaceuticals the speed of action is less important, making this is an attractive approach.

[0255] One can thus create combinatorial libraries of dimeric, trimeric, tetrameric or multimeric toxins/modulators, each native or modified, and directly screen these libraries at the protein level or pan these libraries using genetic packages for improved affinity (avidity, if binding occurs simultaneously at multiple sites) and then characterize the specificity and activity of such multimeric clones by protein expression and purification followed by cell-based activity assays, including patch-clamp assays. The individual modules can be panned and selected separately, in isolation of each other, or they can be designed in each other's presence, such that the new domain is added to a display system as a library that also contain a fixed, active copy that serves as a targeting element for the library and only clones that are significantly better than the fixed, active monomer are selected and characterized.

[0256] FIGS. 46 and 47 show some of the monomeric derivatives that can be made from native (natural) toxins, and some of the multimers that can be made to bind at multiple different binding sites of the target. The linkers are shown as glycine-rich rPEG, but the linkers could be any sequence and could also be optimized using molecular libraries followed by panning. One can create libraries inside the active, native toxin itself, using a variety of mutagenesis strategies as describes above, or one can expand the existing area of contact with the target by creating libraries on the N-terminal or C-terminal side of the active toxin, hoping to create additional contacts with the target. Such libraries can be based on existing toxins with known activity for that site, or they can be or naive 1-, 2-, 3-, 4-disulfide libraries based on unrelated microprotein scaffolds. These additional contact elements can be added on one or both sides of the active domains, and can be directly adjacent to the existing modulatory domain or they can be separated from it by flexible linkers. The initial multimer or the final, improved multimer can be a homomultimer

or a heteromultimer, based on sequence similarity of the domains or based on target specificity of the domains of the multimer. Thus, the monomers that comprise the multimer may bind to the same target sites but have the same or different sequences. With 10-100 different native toxins that are known to bind to each family of channels, and with 2, 3, 4, 5 or 6 domains per clone, display libraries with a huge combinatorial diversity can be created even if one only uses native toxin sequences. Low level synthetic mutagenesis based on amino acid similarity or on phylogenetic substitution rates within the family can be used to create high quality libraries of mutants, of which a very high fraction is expected to retain function, with a high probability of enhanced function in some of the properties of interest.

[0257] The binding capability of the subject MURPs, micropoteins, or toxins to a given ion channel can be measured in terms of Hill Coefficient. Hill Coefficient indicates the stoichiometry of the binding interaction. A Hill coefficient of 2 indicates that 2 inhibitors bind to each channel. One can also assess the allosteric modulation, which is modulation of activity at one site caused by binding at a distant site.

[0258] The biological activity or effect of an ion channel and the ability of the subject MURPs, micropoteins or toxins to regulate an ion channel activity can be assessed using a variety of in vitro and in vivo assays. For instance, methods are available in the art for measuring voltage, measuring current, measuring membrane potential, measuring ion flux, e.g., potassium or rubidium, measuring ion concentration, measuring gating, measuring second messengers and transcription levels, and using e.g., voltage-sensitive dyes, radioactive tracers, and patch-clamp electrophysiology. In particular such assays can be used to test for micropoteins and toxins that can inhibit or activate an ion channel of interest.

[0259] Specifically, potential channel inhibitors or activators can be tested in comparison to a suitable control to examine the extent of modulation. Control samples can also be samples untreated with the candidate activators or inhibitors. Inhibition is present when a given ion channel activity value relative to the control is about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, or even less. IC₅₀ is a commonly used unit (the concentration of inhibitor that reduces the ion channel's activity by 50%) for determining the inhibitory effect. Similar for IC₉₀. Activation of channels is achieved when the select a given ion channel activity value relative to the control is increased by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 500%, or more.

[0260] Changes in ion flux may be assessed by determining changes in polarization (i.e., electrical potential) of the cell or membrane expressing the channel of interest. For instance, one method is to determine changes in cellular polarization is by measuring changes in current (thereby measuring changes in polarization) with voltage-clamp and patch-clamp techniques, e.g., the "cell-attached" mode, the "inside-out" mode, and the "whole cell" mode (see, e.g., Ackerman et al., *New Engl. J. Med.* 336:1575-1595 (1997)). Whole cell currents are conveniently determined using the standard methodology (see, e.g., Hamil et al., *Pflugers. Archiv.* 391:85 (1981)). Other known assays include: radiolabeled rubidium flux assays and fluorescence assays using voltage-sensitive dyes (see, e.g., Vestergaard-Bogind et al., *J. Membrane Biol.* 88:67-75 (1988); Daniel et al., *J. Pharmacol. Meth.* 25:185-193 (1991); Holvevsky et al., *J. Membrane Biology* 137:59-70 (1994)).

[0261] The effects of the candidate MURPs, micropoteins, or toxins upon the function of a channel of interest can be

measured by changes in the electrical currents or ionic flux or by the consequences of changes in currents and flux. The downstream effect of the candidate proteins on ion flux can be varied. Accordingly, any suitable physiological change can be used to assess the influence of a candidate protein on the test channels. The effects of candidate protein can be measured by a toxin binding assay. When the functional consequences are determined using intact cells or animals, one can also measure a variety of effects such as transmitter release (e.g., dopamine), hormone release (e.g., insulin), transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), cell volume changes (e.g., in red blood cells), immunoresponses (e.g., T cell activation), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as Ca^{2+} .

[0262] Other key biological activities of ion channels are ion selectivity and gating. Selectivity is the ability of some channels to discriminate between ion species, allowing some to pass through the pore while excluding others. Gating is the transition between open and closed states. They can be assessed by any of the methods known in the art or disclosed herein

[0263] Yet another biological property that the subject MURP, microprotein, or toxin can be selected for is the frequency of opening and closing of the target channels, called Gating Frequency. Gating Frequency is influenced by voltage (in voltage gated channels, which are opened or closed by changes in membrane voltage) and ligand-binding. The transition rate between open and closed states is typically <10 microseconds but can be increased or decreased by other molecules. The flux rate (current) through the pore when it is open is on the order of 10^7 ions per second for ion channels and much less for coupled exchangers. Following opening, some voltage-gated channels enter an inactivated, non-conducting state in which they are refractory to depolarization.

EXAMPLES

Example

Design of a Glycine-Serine Oligomer Based on Human Sequences

[0264] The human genome data base was searched for sequences that are rich in glycine. Three sequences were identified as suitable donor sequences as shown in Table X.

TABLE X

Donor sequences for GRS design A.			
Accession	Sequences	Amino acid	Protein
NP_009060	GGGSGGSGSGGGG	486-499	zinc finger protein
Q9Y2X9	GSGSGGSGSGG	19-31	zinc finger protein
CAG38801	SGGGSGGSGSGG	7-19	MAP2K4

[0265] Based on the sequences in Table X we designed a glycine rich sequence that contains multiple repeats of the peptide A with sequence GGGSGSGGGGS. Peptide A can be oligomerized to form structures with the formula $(\text{GGGSGSGGGGS})_n$, where n is between 2 and 40. FIG. 5 shows that all possible 9mer subsequences in oligomers of peptide A are contained in at least one of the proteins listed in table 3. Thus oligomers of peptide A do not contain human T

cell epitopes. Inspection of FIG. 5 reveals that GRS based on oligomers of peptide A can begin and end at any of the positions of peptide A.

Example

Design of Glycine-Proline Oligomer Based on Human Sequences

[0266] Glycine rich sequences were designed based on sequence GPGGGGPGGGGGPGGGGGPGGGGGGGGG-PGGGGGGPGGG, which represents amino acids 146-182 of the human class 4 POU domain with accession number NP_006228. FIG. 6 illustrates that oligomers of peptide B with sequence GGGGGPGGGGP can be utilized as GRS. All 9mer subsequences that are contained in peptides with the sequence $(\text{GGGGPGGGGP})_n$ are also contained in the sequence of the POU domain. Thus, such oligomeric sequences do not contain T cell epitopes.

Example

Design of Glycine-Glutamic Acid Oligomer

[0267] Glycine rich sequences can be designed based on the subsequence GAGGEGGGEGGGPGG that is part of the ribosomal protein S6 kinase (accession number BAD92170). For instance, oligomers of peptide C with the sequence GGGGE will form sequences where most 9mer subsequences will be contained in the sequence of ribosomal protein S6 kinase. Thus, oligomeric GRS of the general structure $(\text{GGGGE})_n$ bear a very low risk of containing T cell epitopes.

Example

Identification of Human Hydrophilic Glycine-Rich Sequences

[0268] A data base of human proteins was searched for subsequences that are rich in glycine residues. These subsequences contained at least 50% glycine. Only the following non-glycine residues were allowed to occur in the GRS: ADEHKPRST. 70 subsequences were identified that had a minimum length of 20 amino acids. These subsequences are listed in appendix A. They can be utilized to construct GRS with low immunogenic potential in humans.

Example

Construction of rPEG_J288

[0269] The following example describes the construction of a codon optimized gene encoding a URP sequence with 288 amino acids and the sequence $(\text{GSGGEG})_{48}$. First we constructed a stuffer vector pCW0051 as illustrated in FIG. 40. The sequence of the expression cassette in pCW0051 is shown in FIG. 42. The stuffer vector was based on a pET vector and includes a T7 promoter. The vector encodes a Flag sequence followed by a stuffer sequence that is flanked by BsaI, BbsI, and KpnI sites. The BsaI and BbsI sites were inserted such that they generate compatible overhangs after digestion as illustrated in FIG. 42. The stuffer sequence was followed by a His₆ tag and the gene of green fluorescent protein (GFP). The stuffer sequence contains stop codons and thus *E. coli* cells carrying the stuffer plasmid pCW0051 formed non-fluorescent colonies. The stuffer vector pCW0051 was digested with BsaI and KpnI. A codon library encoding URP sequences of 36 amino acid length was con-

structed as shown in FIG. 41. The URP sequence was designated rPEG_J36 and had the amino acid sequence (GSGGEG)₆. The insert was obtained by annealing synthetic oligonucleotide pairs encoding the amino acid sequence GSGGEGGSGGEG as well as a pair of oligonucleotides that encode an adaptor to the KpnI site. The following oligonucleotides were used: pr_LCW0057 for: AGGTAGTGGWGGW-GARGGWGGWTCYGGWGGAGAAGG, pr_LCW0057rev:

[0270] ACCTCCTTCTCCWCCRGAWCCWC-CYTCWCCWCCACT, pr_3 KpnIstopperFor: AGGT-TCGTCTTCACTCGAGGGTAC, pr_3 KpnIstopperRev: CCTCGAGTGAAGACGA. The annealed oligonucleotide pairs were ligated, which resulted in a mixture of products with varying length that represents the varying number of rPEG_J12 repeats. The product corresponding to the length of rPEG_J36 was isolated from the mixture by agarose gel electrophoresis and ligated into the BsaI/KpnI digested stuffer vector pCW0051. Most of the clones in the resulting library designated LCW0057 showed green fluorescence after induction which shows that the sequence of rPEG_J36 had been ligated in frame with the GFP gene. The process of screening and iterative multimerization of rPEG_J36 sequences is illustrated in FIG. 14. We screened 288 isolates from library LCW0057 for high level of fluorescence. 48 isolates with strong fluorescence were analyzed by PCR to verify the length of the rPEG_J segment and 16 clones were identified that had the expected length of rPEG_J36. This process resulted in a collection of 16 isolates of rPEG_J36, which show high expression and which differ in their codon usage. The isolates were pooled and dimerized using a process outlined in FIG. 40. A plasmid mixture was digested with BsaI/NcoI and a fragment comprising the rPEG_J36 sequence and a part of GFP was isolated. The same plasmid mixture was also digested with BbsI/NcoI and the vector fragment comprising rPEG_J36, most of the plasmid vector, and the remainder of the GFP gene was isolated. Both fragments were mixed, ligated, and transformed into BL21 and isolates were screened for fluorescence. This process of dimerization was repeated two more rounds as outlined in FIG. 14. During each round, we doubled the length of the rPEG_J gene and ultimately obtained a collection of genes that encode rPEG_J288. The amino acid and nucleotide sequence of rPEG_J288 is shown in FIG. 15. It can be seen that the rPEG_J288 module contains segments of rPEG_J36 that differ in their nucleotide sequence despite of having identical amino acid sequence. Thus we minimized internal homology in the gene and as a result we reduced the risk of spontaneous recombination. We cultured *E. coli* BL21 harboring plasmids encoding rPEG_J288 for at least 20 doublings and no spontaneous recombination was observed.

Example

Construction of rPEG_H288

[0271] A library of genes encoding a 288 amino acid URP termed rPEG_H288 was constructed using the same procedure that was used to construct rPEG_J288. rPEG_H288 has the amino acid sequence (GSGGEGGSGGSG)₂₄. The flow chart of the construction process is shown in FIG. 14. The complete amino acid sequence as well as the nucleotide sequence of one isolate of rPEG_H288 as given in FIG. 16.

Example

Serum Stability of rPEG_J288

[0272] A fusion protein containing the an N-terminal Flag tag and the URP sequence rPEG_J288 fused to the N-termi-

nus of green fluorescent protein was incubated in 50% mouse serum at 37 C for 3 days. Samples were withdrawn at various time points and analyzed by SDS PAGE followed by detection using Western analysis. An antibody against the N-terminal flag tag was used for Western detection. Results are shown in FIG. 28, which indicate that a URP sequence of 288 amino acids can be completely stable in serum for at least three days.

Example

Absence of Pre-Existing Antibodies to rPEG_J288 in Serum

[0273] Existence of antibodies against URP would be an indication of a potential immunogenic response to this glycine rich sequence. To test for the presence of existing antibodies in serum, an URP-GFP fusion was subjected to an ELISA by immobilizing URP-GFP on a support and subsequently incubating with 30% serum. The presence of antibodies bound to URP-GFP were detected using an anti-IgG-horse radish peroxidase antibody and substrate. The data are shown in FIG. 29. The data show, that the fusion protein can be detected by antibodies against GFP or Flag but not by murine serum. This indicates that murine serum does not contain antibodies that contain the URP sequence.

Example

Purification of a Fusion Protein Containing rPEG_J288

[0274] We purified a protein with the architecture Flag-rPEG_J288-H6-GFP. The protein was expressed in *E. coli* BL21 in SB medium. Cultures were induced with 0.5 mM IPTG overnight at 18 C. Cells were harvested by centrifugation. The pellet was re-suspended in TBS buffer containing benzonase and a commercial protease inhibitor cocktail. The suspension was heated for 10 min at 75 C in a water bath to lyse the cells. Insoluble material was removed by centrifugation. The supernatant was purified using immobilized metal ion specificity (IMAC) followed by a column with immobilized anti-Flag antibody. FIG. 43 shows PAGE analysis of the purification process. The process yielded protein with at least 90% purity.

Example

Construction of Fusion Protein Between rPEG_J288 and Interferon-Alpha

[0275] A gene encoding human interferon alpha was designed using codon optimization for *E. coli* expression. The synthetic gene was fused with a gene encoding rPEG_J288. A His6 tag was placed at the N-terminus to facilitate detection and purification, of the fusion protein. The amino acid sequence of the fusion protein is given in FIG. 44.

Example

Construction of rPEG_J288-G-CSF Fusion

[0276] A gene encoding human G-CSF was designed using codon optimization for *E. coli* expression. The synthetic gene was fused with a gene encoding rPEG_J288. A His6 tag was placed at the N-terminus to facilitate detection and purification.

tion of the fusion protein. The amino acid sequence of the fusion protein is given in FIG. 44.

Example

Construction of rPEG_J288-hGH Fusion

[0277] A gene encoding human growth hormone was designed using codon optimization for *E. coli* expression. The synthetic gene was fused with a gene encoding rPEG_J288. A His6 tag was placed at the N-terminus to facilitate detection and purification of the fusion protein. The amino acid sequence of the fusion protein is given in FIG. 44.

Example

Expression of Fusion Proteins Between rPEG_J288 and Human Proteins

[0278] The fusion proteins between rPEG_J288 and two human proteins, interferon-alpha and human growth hormone were cloned into a T7 expression vector and transformed into *E. coli* BL21. The cells were grown at 37 C to an optical density of 0.5 OD. Subsequently, the cells were cultured at 18 C for 30 min. Then 0.5 mM IPTG was added and the cultures were incubated in a shaking incubator at 18 C overnight. Cells were harvested by centrifugation and soluble protein was released using BugBuster (Novagen). Both, insoluble and soluble protein fractions were separated by SDS-PAGE and the fusion proteins were detected by Western using and antibody against the N-terminal His6 tag for detection. FIG. 45 shows the Western analysis of the two fusion proteins as well as rPEG_J288-GFP as control. All fusion proteins were expressed and the majority of the protein was in the soluble fraction. This is evidence of the high solubility of rPEG_J288 because most attempts at expression of the interferon-alpha and human growth hormone in the cytosol of *E. coli*, that have been reported in the literature, resulted in the

formation of insoluble inclusion bodies. FIG. 45 shows that the majority of fusion proteins are expressed as full length proteins, i.e. no fragments that would suggest incomplete synthesis or partial protein degradation were detected.

Example

Construction and Binding of aVEGF Multimer

[0279] Libraries of cysteine-constrained peptides were constructed as published [Scholle, M. D., et al. (2005) *Comb Chem High Throughput Screen*, 8: 545-51]. These libraries were panned against human VEGF and two binding modules were identified consisting of amino acid sequences FTCT-NHWCPS or FQCTRHWCP. Oligonucleotides encoding the amino acid sequence FTCTNHWCPS were ligated to a nucleotide sequence encoding the URP sequence rPEG_A36 with the sequence (GGS)12. Subsequently, the fusion sequence was dimerized using restriction enzymes and ligation steps to construct a molecule that contains 4 copies of the VEGF binding module separated by rPEG_A36 fused to GFP. The VEGF binding affinity of fusion proteins containing between zero and four VEGF-binding units were compared in FIG. 30. A fusion protein containing only rPEG_A36 fused to GFP shows no affinity for VEGF. Adding increasing numbers of VEGF binding modules increases affinity of the resulting fusion proteins.

Example

Discovery of 1SS Binding Modules Against Therapeutic Targets

[0280] Random peptide libraries were generated according to Scholle, et al. [Scholle, M. D., et al. (2005) *Comb Chem High Throughput Screen*, 8: 545-51]. The naïve peptide libraries displayed cysteine-constrained peptides with cysteines spaced by 4 to 10 random residues. The library design is illustrated in the table:

TABLE X

Naive 1SS libraries:											
LNG0001	XXXCXXCXXX	X ₃ CX ₂ CX ₃	NNS	NNS	NNS	TGC	NNS	NNS	TGT	NNS	NNS
LNG0002	XXCXXXCXXX	X ₂ CX ₃ CX ₃	NNS	NNS	TGC	NNS	NNS	NNS	TGT	NNS	NNS
LNG0003	XXCXXXXCXX	X ₂ CX ₄ CX ₂	NNS	NNS	TGC	NNS	NNS	NNS	TGT	NNS	NNS
LNG0004	XCXXXXXCXX	X ₁ CX ₅ CX ₂	NNS	TGC	NNS	NNS	NNS	NNS	TGT	NNS	NNS
LNG0005	XCXXXXXXCX	X ₁ CX ₆ CX ₁	NNS	TGC	NNS	NNS	NNS	NNS	NNS	TGT	NNS
LNG0006	CXXXXXXXCX	CX ₇ CX ₁	TGC	NNS	NNS	NNS	NNS	NNS	NNS	TGT	NNS
LNG0007	CXXXXXXXXC	CX ₈ C	TGC	NNS	NNS	NNS	NNS	NNS	NNS	NNS	TGT
LNG0008	CXXXXXXXXC	CX ₉ C	TGC	NNS	NNS	NNS	NNS	NNS	NNS	NNS	TGT
LNG0009	CXXXXXXXXC	CX ₁₀ C	TGC	NNS	NNS	NNS	NNS	NNS	NNS	NNS	NNS
LNG0010	XXXXXXXXXX	X ₆ CX ₂ CX ₆	NNS	NNS	NNS	NNS	NNS	TGC	NNS	NNS	TGT
LNG0011	XXXXXXXXXX	X ₅ CX ₃ CX ₆	NNS	NNS	NNS	NNS	NNS	TGC	NNS	NNS	TGT
LNG0012	XXXXXXXXXX	X ₅ CX ₄ CX ₅	NNS	NNS	NNS	NNS	NNS	TGC	NNS	NNS	TGT

TABLE X-continued

Naive 1SS libraries:											
LNG0013	XXXXXXXXXXXXX ₄ CX ₅ CX ₅	NNS	NNS	NNS	NNS	TGC	NNS	NNS	NNS	NNS	TGT
		NNS	KNS	NNS	NNS	NNS					
LNG0014	XXXXXXXXXXXXX ₄ CX ₆ CX ₄	NNS	NNS	NNS	NNS	TGC	NNS	NNS	NNS	NNS	NNS
		TGT	NNS	NNS	NNS	NNS					
LNG0015	XXXXXXXXXXXXX ₃ CX ₇ CX ₄	NNS	NNS	NNS	TGC	NNS	NNS	NNS	NNS	NNS	NNS
		TGT	NNS	NNS	NNS	NNS					
LNG0016	XXXXXXXXXXXXX ₃ CX ₈ CX ₃	NNS	NNS	NNS	TGC	NNS	NNS	NNS	NNS	NNS	NNS
		NNS	TGT	NNS	NNS	NNS					
LNG0017	XXXXXXXXXXXXX ₂ CX ₉ CX ₃	NNS	NNS	TGC	NNS	NNS	NNS	NNS	NNS	NNS	NNS
		NNS	TGT	NNS	NNS	NNS					
LNG0018	XXXXXXXXXXXXX ₇ CX ₁₀ CX ₂	NNS	NNS	TGC	NNS	NNS	NNS	NNS	NNS	NNS	NNS
		NNS	NNS	TGT	NNS	NNS					

[0281] The libraries were panned against a series of therapeutically relevant targets using the following protocol: Wells on immunosorbent ELISA plates were coated with 5 µg/ml of the target antigen in PBS overnight at 4° C. Coated plates were washed with PBS, and non-specific sites were blocked with Blocking Buffer (PBS containing either 0.5% BSA or 0.5% Ovalbumin) for 2 h at room temperature. The plates were then washed with PBST (PBS containing 0.05% Tween 20), and phage particles at 1-5×10¹²/ml in Binding Buffer (Blocking Buffer containing 0.05% Tween 20) were added to the wells and incubated with shaking for 2 h at room temperature. Wells were then emptied and washed with PBST. Bound phage particles were eluted from the wells by incubation with 100 mM HCl for 10 min at room temperature, transferred to sterile tubes, and neutralized with 1M TRIS base. For infection, log phase *E. Coli* SS320 growing in Super Broth supplemented with 5 µg/ml Tetracycline were added to the neutralized phage eluate, and the culture was incubated with shaking for 30 min at 37° C. Infected cultures were then transferred to larger tubes containing Super Broth with 5 µg/ml Tetracycline and the cultures were incubated with shaking overnight at 37° C. The overnight cultures were cleared of *E. Coli* by centrifugation, and phage were precipitated from the supernatant following the addition of a solution of 20% PEG and 2.5MNaCl to a final PEG concentration of 4%. Precipitated phage were harvested by centrifugation, and the phage pellet was resuspended in 1 ml PBS, cleared of residual *E. Coli* by centrifugation, and transferred to a fresh tube. Phage concentrations were estimated spectrophotometrically and phage was utilized for the next round of selection. Individual clones were screened for target binding affinity after 3 or 4 rounds of phage panning. Individual plaques from phage clones selected during the panning were picked into Super Broth containing 5 µg/ml Tetracycline and grown overnight with shaking at 37° C. ELISA plates were prepared by coating antigen and control proteins (BSA, Ovalbumin, IgG) at 3 µg/ml in PBS overnight at 4° C. The plates were washed with PBS, and blocked with Blocking Buffer (PBS containing 0.5% BSA) for 2 h at room temperature. Overnight cultures were cleared of *E. coli* by centrifugation and the supernatant was diluted 1:10 in Binding Buffer (Blocking Buffer containing 0.05% Tween 20) and transferred to the

ELISA plates after washing with PBST (PBS containing 0.05% Tween 20). The plates were incubated with shaking for 2 h at room temperature. Following washing with PBST, anti-M13-HRP (Pharmacia), 1:5000 dilution in PBS, was added to wells. The plates were incubated with shaking for 30 min at room temperature and washed with PBST, followed by PBS. A substrate solution containing 0.4 mg/ml ABTS and 0.001% H₂O₂ in 50 mM phosphate-citrate buffer was added to the wells, and allowed to develop for 40 min after which the plates were read in a plate reader at 405 nm. These ELISA readings allowed the determination of clone specificity, and antigen-specific clones were sequenced commercially via established methods.

TABLE X

Sequences of EpCAM-specific binding modules	
S Y I C H N C L L S	sNG0017S3.021
L R C W G M L C Y A	sNG0017S3.017
L R C I G Q I C W R	sNG0017S3.022
L K C L Y N I C W V	sNG0017S3.024
R P G M A C S G Q L C W L N S P	sNG001SS3.015
P H A L Q C Y G S L C W P S H L	sNG001SS3.018
R A G I T C H G H L C W P I T D	sNG001SS3.019
R P A L K C I G T L C S L A N P	sNG001SS3.014
P H G L W C H G S L C H Y P L A	sNG001SS3.012
P H G L I C A G S I C F W P P P	sNG001SS3.007
P R N L T C Y G Q I C F Q S Q H	sNG001SS3.011
P H N L A C Q N S I C V R L P R	sNG001SS3.021
P H G L T C T N Q I C F Y G N T	sNG001SS3.006
L F C W G N V C H F	sNG0017S3.006
L T C W G Q V C F R	sNG0017S3.009

TABLE X-continued

Sequences of EpCAM-specific binding modules	
R C P S R V P W C V	sNG0017S3.011
Q L V C G F S D S S R L C Y M R	sNG001SS3.009
L L C Y I T S P G N R L C S P Y	sNG001SS3.022

TABLE X

Sequences of VEGF-specific binding modules	
W E C T Q H W C P S	sNG0025S3.021
A P F F S C S F G F C R D L Q T	sNG0026S3.035
T P Y F R C Q F G F C F D S F S	sNG0026S3.045
N P F F Y C V A G K C V D A P L	sNG0026S3.029
D M R F L C R H G K C H D L P L	sNG0026S3.034
P P F F V C S L G K C R D A H L	sNG0026S3.043
P P Q F Q C V R G K C F D L T F	sNG0026S3.053
I S T F F C S N G S C V D V P A	sNG0026S3.006
P P H F R C F N G S C V D L S R	sNG0026S3.051
N V H F W C H N H K C H D L V S	sNG0026S3.040
L F F K C D V G H G C Y D I K H	sNG0026S3.038
L Y F Q C F P N R G C S T L Q P	sNG0026S3.002
P S F F C S P L L G C R D S L S	sNG0026S3.052
G T P R C N P F R Q F C A I P S	sNG0026S3.032
L C L P L G R W C P	sNG0025S3.016
T S P A C N P F R H F C T L P T	sNG0026S3.058
Q P P I C N P F R Q L C G I P L	sNG0026S3.046
V H T F C N P F R Q M C S L P M	sNG0026S3.027
R M V N C N P F N S W C S L P S	sNG0026S3.001
S K H M C N P F H S W C G V P L	sNG0026S3.047
R W P V C N P F L G Y C G I P N	sNG0026S3.056
S K P T C N V F N S W C S V P L	sNG0026S3.059
R P P A C N L F L S W C S Y D S	sNG0026S3.004
G R S V C N P Y K S W C P V R Q	sNG0026S3.011
A S S C K D S P H F R C L F P L	sNG0026S3.055
L A N C P N S P G F L C L H A V	sNG0026S3.024
P F A C P H S S G F R C L Y N I	sNG0026S3.005
S F T C S L F P S P H C T T L R	sNG0026S3.054
L R L C T Y G G G K Y D C S S T	sNG0026S3.050
G S Y C Q Y R P F S S F C N R S	sNG0026S3.048
C S Y N Q V L G R A C	sNG0025S3.001

TABLE X-continued

Sequences of VEGF-specific binding modules	
P H C R Q H P L D R W M C S P S	sNG0026S3.057
S L C S M F G D T P H W N C V P	sNG0026S3.007
S S C S L F N N T R H W S C T D	sNG0026S3.008

TABLE X

Sequences of CD28-specific binding modules	
T T A Y P D C F W C S L F G P P	sNG0028S3.085
M L D T T I C P W C S L F G P V	sNG0028S3.081
M L X T T I C P W C S L F G P V	sNG0028S3.018
E L L L E R C S W C S L F G P P	sNG0028S3.086
S L S Q Q S C D W C W L F G P P	sNG0028S3.060
K R L L E C G A L C A L F G P P	sNG0028S3.008
H T I L T C D S G F C T L F G P	sNG0028S3.012
N L W H V C H T S L C H S R L A	sNG0028S3.092
N S F Y L C H S S V C G Q L P S	sNG0028S3.082
A G F S C E N Y F F C P P K N L	sNG0028S3.016
S W C T V F G N H D P S C N S R	sNG0028S3.004
C S S N G R W K A H C	sNG0028S3.076
L P N M W R V V V P D V Y D R R	sNG0028S3.068

TABLE X

Sequences of CD28-specific binding modules	
K H Y C F G P K S W T T C A R G	sNG0030S3.096
P W C H L C P G S P S R C C Q P	sNG0030S3.091
P E S K L I S E E D L N G D V S	sNG0030S3.042

TABLE X

Sequences of Tiel-specific binding modules	
I W D R V C R M N T C H Q H S H	sNG0032S3.096
P Y T I F C L H S S C R S S S S	sNG0032S3.087
D W C L T G P N T L S F C P R R	sNG0032S3.031

TABLE X

Sequences of DR4-specific binding modules	
L S T W R C L H D V C W P P L K	sNG0033S3.072

TABLE X

Sequences of DR5-specific binding modules		
V Y L T Q C G A Q L C L K R T N	sNG0034S3.039	
P Y L T S C G D R V C L K R P P	sNG0034S3.001	
P Y L S R C G G R I C M H D R L	sNG0034S3.026	
L K L T P C S H G V C M H R L R	sNG0034S3.087	
Y Y L T N C P K G H C L R R V D	sNG0034S3.080	
L Y L H S C S R G I C L S P R V	sNG0034S3.082	
F S C Q S S F P G R R M C E L R	sNG0034S3.040	
H R C S A H G S S S S F C P G S	sNG0034S3.029	

TABLE X

Sequences of TrkA-specific binding modules		
K T W D C R N S G H C V I T F K	sNG0035S3.074	
A T W D C R D H N F S C V R L S	sNG0035S3.089	

Example

aEpCAM Drug Conjugates

[0282] Anti-EpCAM peptides were isolated from random peptide libraries that were generated according to Scholle, et al. [Scholle, M. D., et al. (2005) *Comb Chem High Throughput Screen*, 8: 545-51] The naïve peptide libraries displayed cysteine-constrained peptides with cysteines spaced by 4 to 10 random residues. After three rounds of affinity selection with the above libraries, several EpCAM specific peptide ligands (EpCam1) were isolated (Table X). The EpCam1 isolates have a conserved cysteine spacing of four amino acids (CXXXXC). EpCam1 peptide ligands were then softly randomized (except cysteine positions) with codons encoding 3-9 residues and moved into a phagemid vector. Phagemid libraries were subsequently affinity selected against EpCAM to isolate peptide ligands optimized for binding (Table X, EpCam2). EpCam2 ligands contain the conserved CXXXXC cysteine spacing. In addition, the majority of anti-EpCam sequences do not contain a lysine residue, which allows for conjugation to free amine groups outside of the binding sequences. Furthermore, anti-EpCam peptide ligands can be genetically fused to URP sequences (of any length) and multimerized using iterative dimerization. The resulting anti-EpCAM MURPs can be used to specifically target EpCAM with increased affinity over monomer sequences. An example of a tetramer EpCAM-URP amino acid sequence is shown in FIG. 31. This sequence contains only two lysine residues that are located in the N-terminal Flag-tag. The side chains of these lysine residues are particularly suitable for drug conjugation.

TABLE X

Anti-EpCam sequences	
Name	Sequence
EpCam 1	LRCWGMLCYA
	LRCIGQICWR
	LKCLYNICWV
	LFCWGNVCHF
	LTCWGVCFR
	RPGMACSGQLCWLNSP
	PHALQCYGSLCWPSHL
	RAGITCHGHLCPITD
	RPALKCIGTLCSLANP
	PHGLWCHGSLCHYPLA
	PHGLICAGSICFWPPP
	PRNLTCYGQICFQSQH
	PHNLACQNSICVRLPR
	PHGLTCTNQCIFYGNT
EpCam 2	HSLTCYGQICWVSNI
	PTLTCYNQVCWVNRT
	PALRCLGQLCWVTPT
	PGLRCLGTLCWVPNR
	RNLTCWNTVCYAYPN
	RGLKCLGQLCWVSSN
	PTLKCSGQICWVPPP
	RNLECLGNVCSLLNQ
	PTLTCLNNLCWVPPQ
	RGLKCSGHLCWVTPQ
	HGLTCHNTVCWVHHP
	HTLECLGNICWVINQ
	HGLTCYNQICWAPRP
	HGLACYNQLCWVNPH
	RGLACQGNICWRLNP
	RAITCLGTLCWPTSP
	LTLECIIGNICYVPHH

Example

Random Sequence Addition

[0283] Binding modules can be affinity matured, or lengthened, by the addition of URP-like linkers and random sequence to the N-terminus, C-terminus, or both N- and C-terminus of the binding sequence. FIG. 32 shows the addition of naïve cysteine-constrained sequences to an anti-EpCAM binding module. Libraries of random sequence additions can be generated using a single-stranded or double-stranded DNA cloning approaches. Once generated, libraries can be affinity selected against the initial target protein or a second protein. For example, an addition library that contains

Construction of a 2SS Buildup Library

Oligo Dilutions

PCR Assembly

PCR Amplification

[0288] The resulting library was panned against VEGF as described below. Several isolates were identified that showed improved binding to VEGF relative to the ISS starting sequence. Binding and expression data are shown in FIG. 38. Sequences and results of Western analysis of buildup clones is shown in FIG. 39.

Phage Panning of Buildup Libraries

[0289] First Round Panning:

[0290] 1) First round, coat 4 wells per library to be screened. Coat the well of a Costar 96-well ELISA plate with 0.25 µg of VEGF₁₂₁ antigen in 25 µl of PBS. Cover the plate with a plate sealer. Coating can be performed overnight at 4°C, or for 1 h at 37°C.

[0291] 2) After shaking out the coating solution, block the well by adding 150 μ l of PBS/BSA 1%. Seal and incubate for 1 h at 37° C.

[0292] 3) After shaking out the blocking solution, add 50 μ l of freshly prepared phage (see library reamplification protocol) to the well. For the first round only, also add 5 μ l of Tween 5%. Seal the plate and incubate for 2 h at 37°C.

[0293] In the meantime, inoculate 2 ml SB medium plus 2 μ l of 5 mg/ml Tetracycline with 2 μ l of an ER 2738 cell preparation and allow growth at 250 rpm and 37° C. for 2.5 h. Grow 1 culture for each library that is screened including negative selections. Take all precautions to avoid a contamination of the culture with phage.

[0294] 4) Shake out the phage solution, add 150 µl of PBS/Tween 0.5% to the well and pipette 5 times vigorously up and down. Wait 5 min, shake out, and repeat this washing step. In the first round, wash in this fashion 5 times, in the second round 10 times, and in the third, fourth and fifth round 15 times.

[0295] 5) After shaking out the final washing solution, add 50 µl of freshly prepared 10 mg/ml trypsin in PBS, seal, and incubate for 30 min at 37° C. Pipette 10 times vigorously up and down and transfer the eluate (4×50 µl in the first round, 2×50 ml in the second round, 1×50 µl in the subsequent rounds) to the prepared 2-ml *E. coli* culture and incubate at room temperature for 15 min.

[0296] 6) Add 6 ml of pre-warmed SB medium, 1.6 μ l of carbenicillin and 6 μ l of 5 mg/ml Tetracycline. Transfer the culture into a 50-ml polypropylene tube.

[0297] 7) Shake the 8-ml culture at 250 rpm and 37° C. for 1 h, add 2.4 μ l 100 mg/ml carbenicillin, and shake for an additional hour at 250 rpm and 37° C.

[0298] 8) Add 1 ml of VCSM13 helper phage and transfer to a 500-ml polypropylene centrifuge bottle. Add 91 ml of pre-warmed (37° C.) SB medium and 46 μ L of 100 mg/ml carbenicillin and 92 μ l of 5 mg/ml Tetracycline. Shake the 100-ml culture at 300 rpm and 37° C. for 1½ to 2 h.

[0299] 9) Add 140 μ l of 50 mg/ml kanamycin and continue shaking at 300 rpm and 37° C. overnight.

[0300] 10) Spin at 4000 rpm for 15 min at 4° C. Transfer the supernatant to a clean 500-ml centrifuge bottle and add add 25 ml of 20% PEG-8000/NaCl 2.5M. Store on ice for 30 min.

[0301] 11) Spin at 9000 rpm for 15 min at 4° C. Discard the supernatant, drain inverted on a paper towel for at least 10 min, and wipe off remaining liquid from the upper part of the centrifuge bottle with a paper towel.

[0302] 12) Resuspend the phage pellet in 2 ml of PBS/BSA 0.5%/Tween 0.5% buffer by pipetting up and down along the side of the centrifuge bottle and transfer to a 2-ml microcentrifuge tube. Resuspend further by pipetting up and down using a 1-ml pipette tip, spin at full speed in a microcentrifuge for 1 min at 4° C., and pass the supernatant through a 0.2- μ m filter into a sterile 2-ml microcentrifuge tube.

[0303] 13) Continue from step 3) for the next round or store the phage preparation at 4° C. Sodium azide may be added to 0.02% (w/v) for long-term storage. Only freshly prepared phage should be used for each round.

[0304] Second Round Panning

[0305] Second round, coat 2 wells per library to be screened. Coat the well of a Costar 96-well ELISA plate with 0.25 μ g of VEGF₁₂₁ antigen in 25 μ l of PBS. Cover the plate with a plate sealer. Coating can be performed overnight at 4° C. or for 1 h at 37° C.

[0306] Also block 2 uncoated wells for each library to be used as negative control for the enrichment ratio calculation.

[0307] Third Round Panning

[0308] Third round, coat 1 well per library to be screened. Coat the well of a Costar 96-well ELISA plate with 0.25 μ g of VEGF₁₂₁ antigen in 25 μ l of PBS. Cover the plate with a plate sealer. Coating can be performed overnight at 4° C. or for 1 h at 37° C.

[0309] Also block 1 uncoated well for each library to be used as negative control for the enrichment ratio calculation.

Example

Solution-Based Panning

[0310] 1. Biotinylate the target protein according to manufacturer.

[0311] 2. Coat a total of 8 wells (per selection) with 1.0 μ g of neutravidin (Pierce) in PBS and incubate overnight at 4° C.

[0312] 3. Block the wells with SuperBlock (Pierce) for 1 h at room temp. Store plate with blocking buffer until needed (in Step 6).

[0313] 4. Use 100 nM of biotinylated target protein and add 1012 phage/ml (in PBST) for a total volume of 100-200 μ l using SuperBlock plus Tween 20 0.05%.

[0314] 5. Tumble phage-target mixture at room temp for at least 1 h.

[0315] 6. Dilute 100 μ l phage-target mix with 700 μ l Super-Block, mix, and add 100 μ l to each of 8 neutravidin-coated wells (from Step 3).

[0316] 7. Incubate for 5 min at room temp.

[0317] 8. Wash 8 \times with PBST.

[0318] 9. Elute phage with 100 μ l of 100 mM HCl for 10 min.

[0319] 10. Neutralize by adding 10 μ l of 1M TRIS pH=8.0.

[0320] 11. Infect cells for plating or amplify phage for a subsequent round of solution panning.

Example

Screening by Phage Elisa for VEGF Positive Clones

[0321] 1) Add 0.5 ml SB containing 50 μ g/ml carbenicillin to 96 deep well plate. Pick one colony and inoculate wells.

[0322] 2) Shake the plate containing the bacterial cultures at 300 rpm o/n at 37° C.

[0323] 3) Prepare 4 ng/ μ l target protein solution in PBS. Add 25 μ l (100 ng) of protein to each well and incubate overnight at 4° C.

[0324] 4) Shake out coated ELISA plates and wash 2 \times with PBS. Add 150 μ l/well PBS+0.5% BSA (blocking buffer). Block for 1 at RT.

[0325] 5) Spin down microtube racks (3000 rpm; 20 min).

[0326] 6) Prepare binding buffer (blocking buffer+0.5% Tween 20). Aliquot 135 μ l binding buffer per well in low protein-binding 96 well plate.

[0327] 7) Shake out wells on ELISA plates and wash 2 times with PBST (PBS+0.5% Tween 20).

[0328] 8) Dilute 15 μ l phage from o/n cultures 1:10 in PBST, mix by pipetting, and transfer 30 μ l to each protein-coated well. Incubate 2 h at RT with gentle shaking.

[0329] 9) Wash plates 6 times with PBST.

[0330] 10) Add 50 μ l antiM13-HRP 1:5000 in binding buffer to the wells. Incubate 30 min with gentle shaking at RT.

[0331] 11) Wash the plates 4 times with PBST, followed by 2 times with H₂O.

[0332] 12) Prepare 6 ml of ABTS solution (5.88 ml of citrate buffer plus 120 μ l ABTS and 2 μ l H₂O₂). Aliquot 50 μ l per well on each ELISA plate

[0333] 13) Incubate at RT and read O.D. at 405 nm using an ELISA plate reader at appropriate time points depending on the signal (up to 1 h)

Example

Dimerization of Binding Modules

[0334] Phage displayed libraries of 10e9 to 10e11 cyclic peptides with 4, 5, 6, 7, 8, 9, 10, 11 and 12 randomized or partially randomized amino acids between the disulfide-bonded cystines, and in some cases additional randomized amino acids on the outside of the cystine pair, were created by standard methods. Panning of these cyclic peptide libraries against a number of targets, including human VEGF, reliably yielded peptides that bound specifically to hVEGF and not to BSA, Ovalbumin or IgG.

Example

Construction and Panning of a Plexin-Based Library

[0335] Two libraries were designed based on the Plexin scaffold. The Pfam protein database was used for phylogenetic alignment of naturally occurring plexin domains as

shown in FIG. 35. The middle part of plexin scaffold (Cys24-Gly25-Trp26-Cys27) is conserved in both library designs and served as a crossover region for N- and C-library generation. The randomization schemes of both plexin libraries are shown in FIG. 36. The two libraries were generated by overlapping two library-encoding oligos at the crossover region and using pull-thru PCR followed by restriction cloning (SfiI/BstXI) and cloning into phagemid vector pMP003. The resulting plexin libraries were designated LMP031 (N terminal library) and LMP032 (C terminal library) and each was represented by a complexity of approximately 5×10^8 independent transformants. For validation, approximately 24 Carb-resistant clones from each unselected library were analyzed by PCR. Clones that gave a correct size fragment (375 bp) were further analyzed by DNA sequencing. Correct full-length plexin sequences were obtained for 50% and 67% of clones derived from LMP031 and LMP032 libraries, respectively.

[0336] The two libraries were mixed together at 50/50 ratio and panned in parallel against VEGF, death receptor Dr4, ErbB2, and HGFR immobilized on 96-well ELISA plates. Four rounds of panning were carried out using 1000 ng of protein target in the first round, 500 ng in the second round, 250 ng in the third round, and 100 ng in the fourth round. After the final round of panning, 192 Carb-resistant clones from each selection were analyzed for binding to 100 ng immobilized protein target, human IgG, Ovalbumin, and BSA by phage ELISA using polyclonal anti-M13 Ab conjugated to horseradish peroxidase for detection. The highest percentage of positive clones was obtained for target DR4 (69%), followed by target ErbB2 (53%), HGFR (13%), and BoNT target (1%). Positive clones were further analyzed by PCR and by DNA sequencing. All clones revealed unique sequences and all but one (against DR4) were derived from LMP032 (C terminal library). Sequences of some of the identified target-selective isolates are shown in FIG. 37.

[0337] For further analysis, an assortment of selected target-specific binders are first subcloned into protein expression vector pVS001, then produced as soluble microproteins, and finally purified by heat lysis. The purified target-specific microproteins are analysed by protein ELISA to confirm the target recognition, by SDS-PAGE to confirm monomer formation, and by surface plasmon resonance to measure their affinities to target. The best clones are used in the next round of library generation to further improve their properties.

Example

Construction of a Snake Toxin-Based Library

[0338] Phage displayed libraries of 10^8 to 10^{10} of 3 finger toxin (3FT) scaffolds with partially randomized amino acids of fingertip 1 and descending part of finger 2 or fingertip 3 and ascending part of finger 2 were created by standard methods.

[0339] Two 3FT scaffolds were used as a template for 3FT library generation (fingers 1 and 2 configuration). The structure of a 3FT scaffold and a multiple sequence alignment of related sequences is shown in FIG. 33. A library was designed such that two surface loops of the toxin are randomized as illustrated in FIG. 34. The library of partially randomized 3FT scaffold was generated by overlapping four library-encoding oligos at the annealing regions and using pull-thru PCR fol-

lowed by restriction cloning (SfiI/BstXI) into phagemid vector pMP003. The resulting 3FT library was designated LMP041.

Example

Grafting of Binding Peptides into Microprotein Scaffolds—Target-specific Peptides-Assisted Randomization

[0340] The aim here is to use the peptides that have been identified to be specific for target of interest in order to generate 3SSplus target-specific binders. This strategy is illustrated by using VEGF-specific peptide transfer into fingertip 1 of 3FT scaffold and by modifying the AA residues of finger 2, which are in close proximity from target specific sequence to generate high affinity VEGF binders. Phage displayed libraries of 10^8 to 10^{10} of 3 finger toxin (3FT) scaffolds with VEGF specific sequence of fingertip 1 and partially randomized descending part of finger 2 was created by standard methods as described in example above except 2 random finger 1 forward primers were replaced by F1-VEGF-specific forward primer encoding the following sequence: P S G P S C H T T N H W P I S A V T C P P.

[0341] The focused (VEGF-specific) 3FT scaffold library with partially randomized finger 2 was generated by overlapping four library-encoding oligos at the annealing regions and using pull-thru PCR followed by restriction cloning (SfiI/BstXI) into phagemid vector pMP003. The resulting 3FT library was designated LMP042.

Example

Plasma Half-Life of an MURP

[0342] The plasma half-life of MURPs can be measured after i.v. or i.p. injection of the MURP into catheterized rats essentially as described by [Pepinsky, R. B., et al. (2001) *J Pharmacol Exp Ther*, 297: 1059-66]. Blood samples can be withdrawn at various time points (5 min, 15 min, 30 min, 1 h, 3 h, 5 h, 1 d, 2 d, 3 d) and the plasma concentration of the MURP can be measured using ELISA. Pharmacokinetic parameters can be calculated using WinNonlin version 2.0 (Scientific Consulting Inc., Apex, N.C.). To analyze the effect of the URP module one can compare on plasma half-life of a protein containing the URP module with the plasma half-life of the same protein lacking the URP module.

Example

Solubility Testing of an MURP

[0343] Solubility of MURPs can be determined by concentrating purified samples of MURPs in physiological buffers like phosphate buffered saline to various concentrations in the range of 0.01 mg/ml to 10 mg/ml. Samples can be incubated for up to several weeks. Samples where the concentration exceeds the solubility of the MURP show precipitation as indicated by turbidity, which can be measured in an absorbance reader. One can remove precipitated material by centrifugation or filtration and measure the concentration of remaining protein in the supernatant using a protein assay like the Bradford assay or by measuring the absorbance at 280 nm. Solubility studies can be accelerated by freezing the samples

at -20 C and subsequent thawing. This process frequently leads to the precipitation of poorly soluble proteins.

Example

Serum Binding Activity of MURPs

[0344] One can coat MURPs of interest into microtiter plates and control proteins in other wells of the plate. Subsequently, one can add serum samples of interest to the wells for 1 hour. Subsequently, the wells can be washed with a plate washer. Bound serum proteins can be detected by adding

antibodies against serum proteins that have been conjugated with enzymes like horse radish peroxidase or alkaline phosphatase for detection. Another way to detect serum binding to MURPs is to add the MURP of interest to serum for about 1 hour to allow binding. Subsequently, one can immunoprecipitate the MURP using an antibody against an epitope in the MURP sequence. The precipitated samples can be analyzed by PAGE and optionally by Western to detect any proteins that co-precipitated with the MURP. One can identify the serum proteins that show co-precipitation by mass spectrometry.

SEQUENCE LISTING

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<400> SEQUENCE: 2

Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Arg Gly Ala Gly Gly
1 5 10 15

<210> SEQ ID NO 3

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Feline Panleukopenia Virus

<400> SEQUENCE: 3

Thr Gly Ser Gly Asn Gly Ser Gly Gly Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly

<210> SEQ ID NO 4

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Canine Parvovirus

<400> SEQUENCE: 4

Thr Gly Ser Gly Asn Gly Ser Gly Gly Gly Gly Gly Gly Ser Gly
1 5 10 15

-continued

Gly

<210> SEQ ID NO 5
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Murine Minute Virus

<400> SEQUENCE: 5

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
1 5 10

<210> SEQ ID NO 6
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Gly Pro Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Gly Pro Gly Gly
1 5 10 15

Gly Gly Pro Gly Gly Gly Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Gly
20 25 30

Gly Pro Gly Gly Gly
35

<210> SEQ ID NO 7
<211> LENGTH: 33
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Gly Ala Gly Gly Ala Gly Ala
20 25 30

Gly

<210> SEQ ID NO 8
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Gly Gly Gly Ser Gly Ser Gly Gly Ala Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser Gly Ser Gly Gly Gly Gly Gly Gly Ala Gly Gly Gly Gly Gly Gly
20 25 30

<210> SEQ ID NO 9
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Gly Asp Gly Gly Gly Ala Gly Gly Gly Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly
20 25

<210> SEQ ID NO 10

-continued

<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10
Gly Ser Gly Ser Gly Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15
Gly Gly Ser Gly Gly Gly Gly Gly Gly
20 25

<210> SEQ ID NO 11
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11
Gly Gly Gly Arg Gly Gly Arg Gly Gly Gly Arg Gly Gly Gly Gly Arg
1 5 10 15
Gly Gly Gly Arg Gly Gly Gly
20

<210> SEQ ID NO 12
<211> LENGTH: 33
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12
Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser
1 5 10 15
Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Gly Ala Gly Gly Ala Gly Ala
20 25 30
Gly

<210> SEQ ID NO 13
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13
Gly Gly Gly Ser Gly Ser Gly Gly Ala Gly Gly Gly Ser Gly Gly Gly
1 5 10 15
Ser Gly Ser Gly Gly Gly Gly Gly Gly Ala Gly Gly Gly Gly Gly Gly Gly
20 25 30

<210> SEQ ID NO 14
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14
Gly Asp Gly Gly Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Ser Gly
1 5 10 15
Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly Gly
20 25

<210> SEQ ID NO 15
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 15

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Gly Pro Gly Pro Gly Pro
1 5 10 15

Gly Gly Gly Gly Gly
20

<210> SEQ ID NO 16

<211> LENGTH: 18

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Gly Glu Gly Gly Gly Gly Gly Gly Glu Gly Gly Gly Ala Gly Gly Gly
1 5 10 15

Ser Gly

<210> SEQ ID NO 17

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Gly Gly Gly Gly Gly Gly Gly Gly Asp Gly Gly Gly
1 5 10

<210> SEQ ID NO 18

<211> LENGTH: 46

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Gly Gly Gly Ser Gly Ser Gly Gly Ala Gly Gly Gly Ser Gly Gly Gly
1 5 10 15

Ser Gly Ser Gly Gly Gly Gly Gly Gly Ala Gly Gly Gly Gly Gly Gly
20 25 30

Ser Ser Gly Gly Gly Ser Gly Thr Ala Gly Gly His Ser Gly
35 40 45

<210> SEQ ID NO 19

<211> LENGTH: 37

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Gly Pro Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Gly Pro Gly Gly
1 5 10 15

Gly Gly Pro Gly Gly Gly Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Gly
20 25 30

Gly Pro Gly Gly Gly
35

<210> SEQ ID NO 20

<211> LENGTH: 35

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Gly Gly Ser Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15

-continued

Ser Gly Ser Gly Gly Gly Gly Ser Thr Gly Gly Gly Gly Gly Thr Ala
20 25 30

Gly Gly Gly
35

<210> SEQ ID NO 21
<211> LENGTH: 33
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Gly Ala Gly Gly Ala Gly Ala
20 25 30

Gly

<210> SEQ ID NO 22
<211> LENGTH: 33
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Gly Ala Gly Gly Ala Gly Ala
20 25 30

Gly

<210> SEQ ID NO 23
<211> LENGTH: 33
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Gly Ala Gly Gly Ala Gly Ala
20 25 30

Gly

<210> SEQ ID NO 24
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Gly His Pro Gly Ser Gly Ser Gly Ser Gly Gly Gly Gly Gly Gly Gly
1 5 10 15

Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly Ala Pro Gly Gly
20 25 30

<210> SEQ ID NO 25
<211> LENGTH: 31
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

-continued

Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15

Gly Gly Gly Ser Gly Ser Thr Gly Gly Gly Ser Gly Ala Gly
20 25 30

<210> SEQ ID NO 26
<211> LENGTH: 31
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Gly Gly Arg Gly Arg Gly Gly Arg Gly Arg Gly Ser Arg Gly Arg Gly
1 5 10 15

Gly Gly Gly Thr Arg Gly Arg Gly Arg Gly Arg Gly Gly Arg Gly
20 25 30

<210> SEQ ID NO 27
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Gly Pro Gly Pro Gly Pro
1 5 10 15

Gly Gly Gly Gly Gly Pro Ser Gly Ser Gly Ser Gly Pro Gly
20 25 30

<210> SEQ ID NO 28
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Arg Gly Gly Gly Gly
1 5 10 15

Arg Gly Gly Gly Arg Gly Gly Gly Gly Glu Gly Gly Gly
20 25

<210> SEQ ID NO 29
<211> LENGTH: 28
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Gly Gly Gly Gly Thr Gly Ser Ser Gly Gly Ser Gly Ser Gly Gly Gly
1 5 10 15

Gly Ser Gly Gly Gly Gly Gly Gly Gly Ser Ser Gly
20 25

<210> SEQ ID NO 30
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Gly Asp Gly Gly Gly Ala Gly Gly Gly Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly
20 25

-continued

<210> SEQ ID NO 31
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Gly Gly Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly
1 5 10 15
Gly Gly Ser Gly Gly Gly Arg Gly Ala Gly Gly
20 25

<210> SEQ ID NO 32
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Gly Gly Gly Ala Ala Gly Ala Gly Gly Gly Gly Ser Gly Ala Gly Gly
1 5 10 15
Gly Ser Gly Gly Ser Gly Gly Arg Gly Thr Gly
20 25

<210> SEQ ID NO 33
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Gly Ala Gly Gly Gly Arg Gly Gly Gly Ala Gly Gly Glu Gly Gly Ala
1 5 10 15
Ser Gly Ala Glu Gly Gly Gly Gly Ala Gly Gly
20 25

<210> SEQ ID NO 34
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Gly Asp Gly Gly Gly Ala Gly Gly Gly Gly Gly Gly Gly Ser Gly
1 5 10 15
Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly
20 25

<210> SEQ ID NO 35
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15
Gly Gly Gly Gly Gly Gly Gly Glu Ala Gly
20 25

<210> SEQ ID NO 36
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 36

Gly Gly Gly Gly Gly Gly Ser Ala Gly Gly Gly Ser Ser Gly Gly Gly
1 5 10 15Pro Gly Gly Gly Gly Gly Gly Ala Gly Gly
20 25

<210> SEQ ID NO 37

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Gly Gly Gly Pro Gly Gly
1 5 10 15Gly Gly Gly Pro Gly Gly Gly Gly Gly
20 25

<210> SEQ ID NO 38

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Gly Arg Gly Gly Ala Gly Ser Gly Gly Ala Gly Ser Gly Ala Ala Gly
1 5 10 15Gly Thr Gly Ser Ser Gly Gly Gly Gly
20 25

<210> SEQ ID NO 39

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser Gly Gly Ser Gly
1 5 10 15Gly Gly Gly Gly Gly Gly Gly Gly Gly
20 25

<210> SEQ ID NO 40

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Gly Gly Ser Gly Gly Gly Arg Gly Gly Ala Ser Gly Pro Gly Ser Gly
1 5 10 15Ser Gly Gly Pro Gly Gly Pro Ala Gly
20 25

<210> SEQ ID NO 41

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Gly Gly His His Gly Asp Arg Gly Gly Gly Arg Gly Gly Arg Gly Gly
1 5 10 15

-continued

Arg Gly Gly Arg Gly Gly Arg Ala Gly
20 25

<210> SEQ ID NO 42
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Gly Ser Arg Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15

Gly Gly Gly Ala Gly Ala Gly Gly Gly
20 25

<210> SEQ ID NO 43
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Gly Gly Arg Gly Gly Arg Gly Pro Gly Glu Pro Gly Gly Arg Gly Arg
1 5 10 15

Ala Gly Gly Ala Glu Gly Arg Gly
20

<210> SEQ ID NO 44
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Gly Gly Gly Gly Gly Asp Ala Gly Gly Ser Gly Asp Ala Gly Gly Ala
1 5 10 15

Gly Gly Arg Ala Gly Arg Ala Gly
20

<210> SEQ ID NO 45
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Gly Gly Gly Arg Gly Gly Arg Gly Gly Gly Arg Gly Gly Gly Gly Arg
1 5 10 15

Gly Gly Gly Arg Gly Gly Gly
20

<210> SEQ ID NO 46
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Gly Gly Ser Gly Gly Gly Gly Gly Ser Ser Gly Gly Arg Gly Ser
1 5 10 15

Gly Gly Gly Ser Ser Gly Gly
20

<210> SEQ ID NO 47
<211> LENGTH: 23

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Gly Ser Gly Pro Gly Thr Gly Gly Gly Gly Ser Gly Ser Gly Gly Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly
20

<210> SEQ ID NO 48
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Gly Ala Arg Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15

Gly Gly Gly Gly Gly Pro Gly
20

<210> SEQ ID NO 49
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15

Gly Gly Gly Gly Gly Asp Gly
20

<210> SEQ ID NO 50
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Gly Gly Thr Arg Gly Gly Thr Arg Gly Gly Thr Arg Gly Gly Asp Arg
1 5 10 15

Gly Arg Gly Arg Gly Ala Gly
20

<210> SEQ ID NO 51
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

Gly Gly Thr Arg Gly Gly Thr Arg Gly Gly Thr Arg Gly Gly Asp Arg
1 5 10 15

Gly Arg Gly Arg Gly Ala Gly
20

<210> SEQ ID NO 52
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly

-continued

1	5	10	15
---	---	----	----

Ala Gly Gly Gly Gly Gly Gly
20

<210> SEQ ID NO 53
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 53

Gly Gly Gly Arg Gly Gly Arg Gly Gly Gly Arg Gly Gly Gly Arg	
1 5 10 15	

Gly Gly Gly Arg Gly Gly Gly
20

<210> SEQ ID NO 54
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 54

Gly Arg Gly Arg Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly	
1 5 10 15	

Gly Arg Gly Gly Gly Gly
20

<210> SEQ ID NO 55
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 55

Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg	
1 5 10 15	

Gly Arg Gly Gly Ala Gly
20

<210> SEQ ID NO 56
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 56

Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly	
1 5 10 15	

Gly Gly Gly Gly Gly Gly
20

<210> SEQ ID NO 57
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 57

Gly Gly Gly Ser Gly Gly Gly His Ser Gly Gly Ser Gly Gly Gly His	
1 5 10 15	

Ser Gly Gly Ser Gly Gly
20

-continued

<210> SEQ ID NO 58
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Gly Ala Gly Ala Gly Gly Gly Gly Gly Gly Gly Ala Gly Gly Gly
1 5 10 15

Gly Ser Ala Gly Ser Gly
 20

<210> SEQ ID NO 59
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Gly Gly Pro Gly Thr Gly Ser Gly Gly Gly Gly Ala Gly Thr Gly Gly
1 5 10 15

Gly Ala Gly Gly Pro Gly
 20

<210> SEQ ID NO 60
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Gly Gly Ala Gly Gly Ala
1 5 10 15

Gly Ser Ala Gly Gly Gly
 20

<210> SEQ ID NO 61
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Gly Gly Asp Gly Gly Gly Ser Ala Gly Gly Gly Ala Gly Gly Gly Ser
1 5 10 15

Gly Gly Gly Ala Gly
 20

<210> SEQ ID NO 62
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Gly Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15

Gly Gly Gly Gly Gly
 20

<210> SEQ ID NO 63
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

-continued

Gly Pro Gly Ala Gly Ala Gly Ser Gly Ala Gly Gly Ser Ser Gly Gly
1 5 10 15

Gly Gly Gly Pro Gly
20

<210> SEQ ID NO 64
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ser Ser Gly Gly Gly
1 5 10 15

Gly Ser Ser Gly Gly
20

<210> SEQ ID NO 65
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Gly Ser Gly Ser Gly Pro Gly Pro Gly Ser Gly Pro Gly Ser Gly Pro
1 5 10 15

Gly His Gly Ser Gly
20

<210> SEQ ID NO 66
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Gly Pro Gly Pro Gly Pro Gly Pro Gly Pro Gly Pro Gly Pro Gly Pro
1 5 10 15

Gly Pro Gly Pro Gly
20

<210> SEQ ID NO 67
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Gly Ala Gly Ser Gly Gly Gly Gly Ala Ala Gly Ala Gly Ala Gly Ser
1 5 10 15

Ala Gly Gly Gly Gly
20

<210> SEQ ID NO 68
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Gly Ala Gly Ser Gly Gly Gly Gly Ala Ala Gly Ala Gly Ala Gly Ser
1 5 10 15

Ala Gly Gly Gly Gly
20

-continued

<210> SEQ ID NO 69
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Gly Gly Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Gly Gly
20

<210> SEQ ID NO 70
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg
1 5 10 15

Gly Arg Gly Arg Gly
20

<210> SEQ ID NO 71
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Gly Gly Gly Gly Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Gly
20

<210> SEQ ID NO 72
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Gly Gly Glu Glu Gly Gly Ala Ser Gly Gly Gly Pro Gly Ala Gly Ser
1 5 10 15

Gly Ser Ala Gly Gly
20

<210> SEQ ID NO 73
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Gly Ser Gly Ser Gly Pro Gly Pro Gly Ser Gly Pro Gly Ser Gly Pro
1 5 10 15

Gly His Gly Ser Gly
20

<210> SEQ ID NO 74
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 74

Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg
1 5 10 15Gly Arg Gly Arg Gly
20

<210> SEQ ID NO 75

<211> LENGTH: 21

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Gly Gly Gly Gly Gly Gly Gly Gly Gly Asp Gly Gly Gly Arg Arg Gly Arg
1 5 10 15Gly Arg Gly Arg Gly
20

<210> SEQ ID NO 76

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Gly Gly Pro Gly Gly Pro Gly Gly Gly Gly Ala Gly Gly Pro Gly Gly
1 5 10 15Ala Gly Ala Gly
20

<210> SEQ ID NO 77

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Gly Thr Gly Gly Gly Gly Ser Thr Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15Ser Gly His Gly
20

<210> SEQ ID NO 78

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Gly Pro Ala Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15Gly Gly Gly Gly
20

<210> SEQ ID NO 79

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Gly Gly Thr Gly Gly Ser Ser Gly Ser Ser Gly Ser Gly Ser Gly Gly
1 5 10 15

-continued

Gly Arg Arg Gly
20

<210> SEQ ID NO 80
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Gly Gly Thr Gly Gly Ser Ser Gly Ser Ser Gly Ser Gly Ser Gly Gly
1 5 10 15

Gly Arg Arg Gly
20

<210> SEQ ID NO 81
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Gly Ser Gly Thr Gly Thr Thr Gly Ser Ser Gly Ala Gly Gly Pro Gly
1 5 10 15

Thr Pro Gly Gly
20

<210> SEQ ID NO 82
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

Gly Gly Ser Gly Gly Gly Ala Ala Gly Gly Gly Ala Gly Gly Ala Gly
1 5 10 15

Ala Gly Ala Gly
20

<210> SEQ ID NO 83
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Gly Gly Ser Gly Gly Gly Ala Ala Gly Gly Gly Ala Gly Gly Ala Gly
1 5 10 15

Ala Gly Ala Gly
20

<210> SEQ ID NO 84
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Gly Ser Ser Gly Gly Gly Gly Gly Gly Ala Gly Ala Ala Gly Gly Ala
1 5 10 15

Gly Gly Ala Gly
20

<210> SEQ ID NO 85
<211> LENGTH: 20

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Gly Pro Gly Pro Ser Gly Gly Pro Gly Gly Gly Gly Gly Gly Gly
1 5 10 15

Gly Gly Gly Gly
20

<210> SEQ ID NO 86
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Ala
1 5 10 15

Gly Ala Gly Gly
20

<210> SEQ ID NO 87
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg Gly Arg
1 5 10 15

Gly Arg Gly Gly
20

<210> SEQ ID NO 88
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Gly Ser Ala Gly Gly Ser Ser Gly Ala Ala Gly Ala Ala Gly Gly Gly
1 5 10 15

Ala Gly Ala Gly
20

<210> SEQ ID NO 89
<211> LENGTH: 600
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: This sequence may encompass 4 to 200
"Ser-Ser-Asp"
repeating units

<400> SEQUENCE: 89

Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser
1 5 10 15

Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser
20 25 30

Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp
35 40 45

-continued

Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
50						55						60			
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser
65					70					75					80
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp
			85						90					95	
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
		100						105					110		
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser
	115						120					125			
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp
	130					135						140			
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
145					150					155					160
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser
				165					170					175	
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp
		180						185					190		
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
	195						200					205			
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser
	210						215					220			
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp
225					230					235					240
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
				245						250				255	
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser
		260						265					270		
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp
	275						280					285			
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
	290						295					300			
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser
305					310					315					320
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp
				325						330				335	
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
		340						345					350		
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser
		355						360				365			
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp
	370						375					380			
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
385					390					395					400
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser
				405						410				415	
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp
		420						425					430		
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser
	435						440						445		

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Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser
 450          455          460

Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp
465          470          475          480

Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser
          485          490          495

Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser
 500          505          510

Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp
 515          520          525

Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser
 530          535          540

Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser
545          550          555          560

Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp
          565          570          575

Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser
 580          585          590

Ser Asp Ser Ser Asp Ser Ser Asp
 595          600

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<210> SEQ ID NO 90
<211> LENGTH: 1200
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: This sequence may encompass 4 to 200
      "Ser-Ser-Asp-Ser-Ser-Asn" repeating units

<400> SEQUENCE: 90

```

```

Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser
1          5          10          15

Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser
 20          25          30

Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn
 35          40          45

Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser
 50          55          60

Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser
65          70          75          80

Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn
 85          90          95

Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser
100          105          110

Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser
115          120          125

Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn
130          135          140

Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser
145          150          155          160

Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn Ser Ser
165          170          175

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Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
			180						185						190
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser
		195						200						205	
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser
	210						215						220		
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
225					230						235				240
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser
					245				250					255	
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser
					260				265					270	
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
			275						280				285		
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser
	290						295					300			
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser
305							310				315				320
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
					325					330				335	
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser
					340					345				350	
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser
					355					360				365	
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
							375					380			
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser
385							390				395				400
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser
					405					410				415	
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
					420					425				430	
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser
					435					440				445	
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser
					450					455				460	
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
465							470				475				480
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser
					485					490				495	
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser
					500					505				510	
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
					515					520				525	
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser
					530					535				540	
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser
545							550				555				560
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
					565					570					575

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Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	580	585	590
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	595	600	605
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	610	615	620
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	625	630	635
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	645	650	655
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	660	665	670
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	675	680	685
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	690	695	700
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	705	710	715
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	725	730	735
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	740	745	750
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	755	760	765
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	770	775	780
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	785	790	795
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	805	810	815
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	820	825	830
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	835	840	845
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	850	855	860
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	865	870	875
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	885	890	895
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	900	905	910
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	915	920	925
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	930	935	940
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	945	950	955
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	965	970	975
Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser			

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980				985				990							
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
		995				1000				1005					
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp
	1010				1015					1020					
Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
	1025				1030					1035					
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp
	1040				1045					1050					
Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
	1055				1060					1065					
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp
	1070				1075					1080					
Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
	1085				1090					1095					
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp
	1100				1105					1110					
Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
	1115				1120					1125					
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp
	1130				1135					1140					
Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
	1145				1150					1155					
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp
	1160				1165					1170					
Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn
	1175				1180					1185					
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Ser	Asp	Ser	Ser	Asn			
	1190				1195					1200					

<210> SEQ ID NO 91

<211> LENGTH: 600

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<220> FEATURE:

<223> OTHER INFORMATION: This sequence may encompass 4 to 200 "Ser-Ser-Glu" repeating units

<400> SEQUENCE: 91

Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser
1			5					10						15	
Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser
		20					25						30		
Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu
		35					40					45			
Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser
		50					55					60			
Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser
	65					70				75					80
Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu
			85						90						95

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Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
100 105 110

Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser
115 120 125

Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu
130 135 140

Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
145 150 155 160

Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser
165 170 175

Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu
180 185 190

Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
195 200 205

Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser
210 215 220

Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu
225 230 235 240

Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
245 250 255

Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser
260 265 270

Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu
275 280 285

Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
290 295 300

Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser
305 310 315 320

Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu
325 330 335

Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
340 345 350

Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser
355 360 365

Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu
370 375 380

Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
385 390 395 400

Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser
405 410 415

Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu
420 425 430

Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
435 440 445

Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser
450 455 460

Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu
465 470 475 480

Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser Ser Glu Ser
485 490 495

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Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	
			500					505						510		
Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	
		515					520					525				
Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	
	530					535					540					
Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	
545					550					555						560
Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	
			565						570					575		
Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu	Ser	
		580						585						590		
Ser	Glu	Ser	Ser	Glu	Ser	Ser	Glu									
		595					600									

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<210> SEQ ID NO 92
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (22)..(22)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)..(24)

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<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro

<400> SEQUENCE: 92

Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa
1 5 10 15

Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa Gly Xaa
 20 25 30

Gly Xaa Gly Xaa Gly Xaa Gly Xaa
 35 40

<210> SEQ ID NO 93
<211> LENGTH: 39
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (18)..(18)

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<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (39)..(39)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro

<400> SEQUENCE: 93

Gly Gly Xaa Gly Gly Xaa Gly Gly Xaa Gly Gly Xaa Gly Gly Xaa Gly
1          5          10         15

Gly Xaa Gly Gly Xaa Gly Gly Xaa Gly Gly Xaa Gly Gly Xaa Gly Gly
20         25         30

Xaa Gly Gly Xaa Gly Gly Xaa
35

<210> SEQ ID NO 94
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)..(24)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)..(28)

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<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro

<400> SEQUENCE: 94

Gly Gly Gly Xaa Gly Gly Gly Xaa Gly Gly Gly Xaa Gly Gly Gly Xaa
1 5 10 15

Gly Gly Gly Xaa Gly Gly Gly Xaa Gly Gly Gly Xaa Gly Gly Gly Xaa
 20 25 30

Gly Gly Gly Xaa Gly Gly Gly Xaa
 35 40

<210> SEQ ID NO 95
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro

<400> SEQUENCE: 95

Gly Gly Gly Gly Xaa Gly Gly Gly Gly Xaa Gly Gly Gly Gly Xaa Gly
1 5 10 15

Gly Gly Gly Xaa Gly Gly Gly Gly Xaa Gly Gly Gly Gly Xaa Gly Gly
 20 25 30

Gly Gly Xaa Gly Gly Gly Gly Xaa
 35 40

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<210> SEQ ID NO 96
<211> LENGTH: 315
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(20)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (22)..(41)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (43)..(62)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (63)..(63)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (64)..(83)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (84)..(84)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (85)..(104)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (105)..(105)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (106)..(125)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (126)..(126)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (127)..(146)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (147)..(147)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (148)..(167)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (168)..(168)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (169)..(188)

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<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (189) .. (189)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (190) .. (209)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (210) .. (210)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (211) .. (230)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (231) .. (231)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (232) .. (251)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (252) .. (252)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (253) .. (272)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (273) .. (273)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (273) .. (293)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (294) .. (294)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (295) .. (314)
<223> OTHER INFORMATION: This region may encompass 1 to 20 Gly residues
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (315) .. (315)
<223> OTHER INFORMATION: Ser, Asp, Glu, Thr or Pro

<400> SEQUENCE: 96

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
1 5 10 15
Gly Gly Gly Gly Xaa Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
20 25 30
Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Xaa Gly Gly Gly Gly Gly
35 40 45
Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Xaa Gly
50 55 60
Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
65 70 75 80
Gly Gly Gly Xaa Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
85 90 95
Gly Gly Gly Gly Gly Gly Gly Gly Xaa Gly Gly Gly Gly Gly Gly Gly
100 105 110

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Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Xaa Gly Gly
115 120 125

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
130 135 140

Gly Gly Xaa Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
145 150 155 160

Gly Gly Gly Gly Gly Gly Gly Xaa Gly Gly Gly Gly Gly Gly Gly Gly
165 170 175

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Xaa Gly Gly Gly
180 185 190

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
195 200 205

Gly Xaa Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
210 215 220

Gly Gly Gly Gly Gly Gly Xaa Gly Gly Gly Gly Gly Gly Gly Gly Gly
225 230 235 240

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Xaa Gly Gly Gly Gly
245 250 255

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
260 265 270

Xaa Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
275 280 285

Gly Gly Gly Gly Gly Xaa Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly
290 295 300

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Xaa
305 310 315

<210> SEQ ID NO 97
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
6xHis tag

<400> SEQUENCE: 97

His His His His His His
1 5

<210> SEQ ID NO 98
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 98

Ser Lys Val Ile Leu Phe Glu
1 5

<210> SEQ ID NO 99
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

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<400> SEQUENCE: 99

Ala Arg Ala Arg Ala Arg
1 5

<210> SEQ ID NO 100

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 100

Asp Ala Asp Ala Asp Ala
1 5

<210> SEQ ID NO 101

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 101

Ser Lys Val Ile Leu Phe
1 5

<210> SEQ ID NO 102

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 102

Arg Ala Arg Ala Arg Ala
1 5

<210> SEQ ID NO 103

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly
1 5 10

<210> SEQ ID NO 104

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

Gly Ser Gly Ser Gly Gly Gly Ser Gly Gly
1 5 10

<210> SEQ ID NO 105

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 105

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly
1 5 10

<210> SEQ ID NO 106

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 106

Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> SEQ ID NO 107

<211> LENGTH: 440

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<220> FEATURE:

<223> OTHER INFORMATION: This sequence may encompass 2 to 40

"Gly-Gly-Gly-Ser-

Gly-Ser-Gly-Gly-Gly-Gly-Ser" repeating units

<400> SEQUENCE: 107

Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
1 5 10 15

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly
20 25 30

Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
35 40 45

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly
50 55 60

Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
65 70 75 80

Ser Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Gly
85 90 95

Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Ser Gly Gly
100 105 110

Gly Ser Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly
115 120 125

Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Ser Gly
130 135 140

Gly Gly Ser Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser
145 150 155 160

Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Ser
165 170 175

Gly Gly Gly Ser Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly
180 185 190

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly
195 200 205

Ser Gly Gly Ser Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
210 215 220

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Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly
 225 230 235 240
 Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 245 250 255
 Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly
 260 265 270
 Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly
 275 280 285
 Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly
 290 295 300
 Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly
 305 310 315 320
 Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser
 325 330 335
 Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser
 340 345 350
 Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
 355 360 365
 Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly
 370 375 380
 Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser
 385 390 395 400
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly
 405 410 415
 Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
 420 425 430
 Ser Gly Ser Gly Gly Gly Gly Ser
 435 440

<210> SEQ ID NO 108

<211> LENGTH: 37

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Gly Pro Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Pro Gly Gly
 1 5 10 15
 Gly Gly Pro Gly Gly Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly
 20 25 30
 Gly Pro Gly Gly Gly
 35

<210> SEQ ID NO 109

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 109

Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Pro
 1 5 10

<210> SEQ ID NO 110

<211> LENGTH: 16

-continued

<212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Gly Ala Gly Gly Glu Gly Gly Gly Gly Glu Gly Gly Gly Pro Gly Gly
 1 5 10 15

<210> SEQ ID NO 111
 <211> LENGTH: 5
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 111

Gly Gly Gly Gly Glu
 1 5

<210> SEQ ID NO 112
 <211> LENGTH: 62
 <212> TYPE: PRT
 <213> ORGANISM: Laticauda semifasciata

<400> SEQUENCE: 112

Arg Ile Cys Phe Asn His Gln Ser Ser Gln Pro Gln Thr Thr Lys Thr
 1 5 10 15
 Cys Ser Pro Gly Glu Ser Ser Cys Tyr Asn Lys Gln Trp Ser Asp Phe
 20 25 30
 Arg Gly Thr Ile Ile Glu Arg Gly Cys Gly Cys Pro Thr Val Lys Pro
 35 40 45
 Gly Ile Lys Leu Ser Cys Cys Glu Ser Glu Val Cys Asn Asn
 50 55 60

<210> SEQ ID NO 113
 <211> LENGTH: 288
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 113

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
 1 5 10 15
 Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
 20 25 30
 Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
 35 40 45
 Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
 50 55 60
 Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
 65 70 75 80
 Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
 85 90 95
 Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
 100 105 110
 Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
 115 120 125

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Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
130 135 140

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
145 150 155 160

Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
165 170 175

Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
180 185 190

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
195 200 205

Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
210 215 220

Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
225 230 235 240

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
245 250 255

Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
260 265 270

Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
275 280 285

<210> SEQ ID NO 114
<211> LENGTH: 36
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 114

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
1 5 10 15

Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
20 25 30

Gly Gly Glu Gly
35

<210> SEQ ID NO 115
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 115

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
1 5 10

<210> SEQ ID NO 116
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 116

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aggtagtggw ggwgargggw gwtcyggwgg agaagg 36

<210> SEQ ID NO 117
 <211> LENGTH: 36
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 oligonucleotide

<400> SEQUENCE: 117

acctccttct ccwccrgawc cwccytccwcc wccact 36

<210> SEQ ID NO 118
 <211> LENGTH: 24
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 oligonucleotide

<400> SEQUENCE: 118

aggttcgtct tcactcgagg gtac 24

<210> SEQ ID NO 119
 <211> LENGTH: 16
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 oligonucleotide

<400> SEQUENCE: 119

cctcgagtga agacga 16

<210> SEQ ID NO 120
 <211> LENGTH: 288
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide

<400> SEQUENCE: 120

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 1 5 10 15
 Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
 20 25 30
 Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
 35 40 45
 Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 50 55 60
 Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
 65 70 75 80
 Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Ser Gly Gly Ser Gly
 85 90 95
 Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 100 105 110
 Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
 115 120 125

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Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
 130 135 140
 Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 145 150 155 160
 Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
 165 170 175
 Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
 180 185 190
 Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 195 200 205
 Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
 210 215 220
 Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
 225 230 235 240
 Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 245 250 255
 Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
 260 265 270
 Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
 275 280 285

<210> SEQ ID NO 121
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 peptide

<400> SEQUENCE: 121

Phe Thr Cys Thr Asn His Trp Cys Pro Ser
 1 5 10

<210> SEQ ID NO 122
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 peptide

<400> SEQUENCE: 122

Phe Gln Cys Thr Arg His Trp Cys Pro Ile
 1 5 10

<210> SEQ ID NO 123
 <211> LENGTH: 36
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 peptide

<400> SEQUENCE: 123

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
 1 5 10 15
 Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
 20 25 30
 Ser Gly Gly Ser

-continued

35

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<210> SEQ ID NO 124
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13)..(14)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (22)..(23)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (25)..(26)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(29)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 124
nnsnnnnnst gcnnnnnnstg tnnnnnnns
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30

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<210> SEQ ID NO 125
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<221> NAME/KEY: modified_base
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<220> FEATURE:
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<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

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nnsnnstgcn nsnnnsnnstg tnnnsnnsns

30

<210> SEQ ID NO 126
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<213> ORGANISM: Artificial Sequence
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oligonucleotide
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (10)..(11)
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<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (19)..(20)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (25)..(26)
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<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 126

nnsnnstgcn nsnnnsnnstg stgtnnnsns

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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (13)..(14)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19)..(20)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (25)..(26)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 127

nnstgcnnsn nnnnsnnnnn stgtnnnnns

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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (19)..(20)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (28)..(29)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 128

nnstgcnnsn nnnnsnnnnn snnstgtnnns

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<210> SEQ ID NO 129
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13)..(14)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19)..(20)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (22)..(23)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(29)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 129

tgcnnnsnnsn nsnnnsnnsnn snnstgttnns

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<210> SEQ ID NO 130
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<212> TYPE: DNA
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<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19)..(20)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (22)..(23)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (25)..(26)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 130

tgcnnsnnsn nsnnnsnnnn snnsnnstgt

30

<210> SEQ ID NO 131
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13)..(14)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (19)..(20)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (22)..(23)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (25)..(26)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(29)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 131

tgcnnsnnsn nsnnnsnnnn snnsnnnsns tgt

33

<210> SEQ ID NO 132
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base

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<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (19)..(20)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (31)..(32)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 132

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tgcnnnsnnsn nsnnsnnsnn snnsnnsnns nnstgt

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36

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (13)..(14)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (22)..(23)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:

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<221> NAME/KEY: modified_base
<222> LOCATION: (25)..(26)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(32)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(35)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (37)..(38)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (40)..(41)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (43)..(44)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (46)..(47)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

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<400> SEQUENCE: 133

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nnnnnnnnnn nnnnnnnstg cnnnnnnstg nnnnnnnnnn nnnnnnnn

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48

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<210> SEQ ID NO 134
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (22)..(23)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (25)..(26)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(35)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (37)..(38)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (40)..(41)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (43)..(44)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (46)..(47)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 134

nnnnnnnnnn nnnnstgcnn snnnnnstgt nnnnnnnnnn nnnnnnnn

48

<210> SEQ ID NO 135
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(29)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(35)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (37)..(38)

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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (40)..(41)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (43)..(44)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (46)..(47)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 135

nnnnnnnnnn nnnnstgcnn snnnnnnnnn tgnnnnnnnn nnnnnnnn

48

<210> SEQ ID NO 136
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16)..(17)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19)..(20)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (22)..(23)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<221> NAME/KEY: modified_base
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<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (37)..(38)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (40)..(41)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base

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<222> LOCATION: (43)..(44)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (46)..(47)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 136

nnnnnnnnnn nstgcnnnnn snnnnnnnnn tgtnnnnnnn nnnnnnnn

48

<210> SEQ ID NO 137
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (4)..(5)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (7)..(8)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (16)..(17)
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

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<400> SEQUENCE: 137

nnnnnnnnn nstgcnnnnn snnnnnnns nnstgtnnn nsnnnnns

48

<210> SEQ ID NO 138
<211> LENGTH: 48
<212> TYPE: DNA
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 138

nnnnnnnnst gcnnnnnnn snnnnnnns nnstgtnnn nsnnnnns

48

<210> SEQ ID NO 139
<211> LENGTH: 48

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<212> TYPE: DNA
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (46)..(47)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 139

nnnnnnnnst gcnnnnnnnn snnnnnnnns nnnnnstgtn nnnnnnns

48

<210> SEQ ID NO 140
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base

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<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 140

nnnnnstgcn nnnnsnnnnn snnnsnnns nnsnnstgtn nnnnsnns

48

<210> SEQ ID NO 141
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:

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<221> NAME/KEY: modified_base
<222> LOCATION: (10)..(11)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<220> FEATURE:
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
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<222> LOCATION: (46)..(47)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 141

nnnnstgcn nnnnnnnnnn snnnnnnnns nnnnnnnnst gtnnnnns

48

<210> SEQ ID NO 142
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 142

Ser Tyr Ile Cys His Asn Cys Leu Leu Ser
1 5 10

<210> SEQ ID NO 143
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 143

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Leu Arg Cys Trp Gly Met Leu Cys Tyr Ala
1 5 10

<210> SEQ ID NO 144
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 144

Leu Arg Cys Ile Gly Gln Ile Cys Trp Arg
1 5 10

<210> SEQ ID NO 145
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 145

Leu Lys Cys Leu Tyr Asn Ile Cys Trp Val
1 5 10

<210> SEQ ID NO 146
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 146

Arg Pro Gly Met Ala Cys Ser Gly Gln Leu Cys Trp Leu Asn Ser Pro
1 5 10 15

<210> SEQ ID NO 147
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 147

Pro His Ala Leu Gln Cys Tyr Gly Ser Leu Cys Trp Pro Ser His Leu
1 5 10 15

<210> SEQ ID NO 148
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 148

Arg Ala Gly Ile Thr Cys His Gly His Leu Cys Trp Pro Ile Thr Asp
1 5 10 15

<210> SEQ ID NO 149

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<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 149

Arg Pro Ala Leu Lys Cys Ile Gly Thr Leu Cys Ser Leu Ala Asn Pro
1 5 10 15

<210> SEQ ID NO 150
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 150

Pro His Gly Leu Trp Cys His Gly Ser Leu Cys His Tyr Pro Leu Ala
1 5 10 15

<210> SEQ ID NO 151
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 151

Pro His Gly Leu Ile Cys Ala Gly Ser Ile Cys Phe Trp Pro Pro Pro
1 5 10 15

<210> SEQ ID NO 152
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 152

Pro Arg Asn Leu Thr Cys Tyr Gly Gln Ile Cys Phe Gln Ser Gln His
1 5 10 15

<210> SEQ ID NO 153
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 153

Pro His Asn Leu Ala Cys Gln Asn Ser Ile Cys Val Arg Leu Pro Arg
1 5 10 15

<210> SEQ ID NO 154
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 154

Pro His Gly Leu Thr Cys Thr Asn Gln Ile Cys Phe Tyr Gly Asn Thr
1 5 10 15

<210> SEQ ID NO 155

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 155

Leu Phe Cys Trp Gly Asn Val Cys His Phe
1 5 10

<210> SEQ ID NO 156

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 156

Leu Thr Cys Trp Gly Gln Val Cys Phe Arg
1 5 10

<210> SEQ ID NO 157

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 157

Arg Cys Pro Ser Arg Val Pro Trp Cys Val
1 5 10

<210> SEQ ID NO 158

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 158

Gln Leu Val Cys Gly Phe Ser Asp Ser Ser Arg Leu Cys Tyr Met Arg
1 5 10 15

<210> SEQ ID NO 159

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 159

Leu Leu Cys Tyr Ile Thr Ser Pro Gly Asn Arg Leu Cys Ser Pro Tyr
1 5 10 15

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<210> SEQ ID NO 160
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 160

Trp	Glu	Cys	Thr	Gln	His	Trp	Cys	Pro	Ser
1				5				10	

<210> SEQ ID NO 161
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 161

Ala	Pro	Phe	Phe	Ser	Cys	Ser	Phe	Gly	Phe	Cys	Arg	Asp	Leu	Gln	Thr
1				5				10					15		

<210> SEQ ID NO 162
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 162

Thr	Pro	Tyr	Phe	Arg	Cys	Gln	Phe	Gly	Phe	Cys	Phe	Asp	Ser	Phe	Ser
1				5				10					15		

<210> SEQ ID NO 163
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 163

Asn	Pro	Phe	Phe	Tyr	Cys	Val	Ala	Gly	Lys	Cys	Val	Asp	Ala	Pro	Leu
1				5				10					15		

<210> SEQ ID NO 164
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 164

Asp	Met	Arg	Phe	Leu	Cys	Arg	His	Gly	Lys	Cys	His	Asp	Leu	Pro	Leu
1				5				10					15		

<210> SEQ ID NO 165
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 165

Pro Pro Phe Phe Val Cys Ser Leu Gly Lys Cys Arg Asp Ala His Leu
1 5 10 15

<210> SEQ ID NO 166

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 166

Pro Pro Gln Phe Gln Cys Val Arg Gly Lys Cys Phe Asp Leu Thr Phe
1 5 10 15

<210> SEQ ID NO 167

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 167

Ile Ser Thr Phe Phe Cys Ser Asn Gly Ser Cys Val Asp Val Pro Ala
1 5 10 15

<210> SEQ ID NO 168

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 168

Pro Pro His Phe Arg Cys Phe Asn Gly Ser Cys Val Asp Leu Ser Arg
1 5 10 15

<210> SEQ ID NO 169

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 169

Asn Val His Phe Trp Cys His Asn His Lys Cys His Asp Leu Val Ser
1 5 10 15

<210> SEQ ID NO 170

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 170

Leu Phe Phe Lys Cys Asp Val Gly His Gly Cys Tyr Asp Ile Lys His

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1	5	10	15
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<210> SEQ ID NO 171
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 171

Leu Tyr Phe Gln Cys Phe Pro Asn Arg Gly Cys Ser Thr Leu Gln Pro
1 5 10 15

<210> SEQ ID NO 172
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 172

Pro Ser Phe Phe Cys Ser Pro Leu Leu Gly Cys Arg Asp Ser Leu Ser
1 5 10 15

<210> SEQ ID NO 173
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 173

Gly Thr Pro Arg Cys Asn Pro Phe Arg Gln Phe Cys Ala Ile Pro Ser
1 5 10 15

<210> SEQ ID NO 174
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 174

Leu Cys Leu Pro Leu Gly Arg Trp Cys Pro
1 5 10

<210> SEQ ID NO 175
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 175

Thr Ser Pro Ala Cys Asn Pro Phe Arg His Phe Cys Thr Leu Pro Thr
1 5 10 15

<210> SEQ ID NO 176
<211> LENGTH: 16
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 176

Gln Pro Pro Ile Cys Asn Pro Phe Arg Gln Leu Cys Gly Ile Pro Leu
1 5 10 15

<210> SEQ ID NO 177
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 177

Val His Thr Phe Cys Asn Pro Phe Arg Gln Met Cys Ser Leu Pro Met
1 5 10 15

<210> SEQ ID NO 178
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 178

Arg Met Val Asn Cys Asn Pro Phe Asn Ser Trp Cys Ser Leu Pro Ser
1 5 10 15

<210> SEQ ID NO 179
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 179

Ser Lys His Met Cys Asn Pro Phe His Ser Trp Cys Gly Val Pro Leu
1 5 10 15

<210> SEQ ID NO 180
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 180

Arg Trp Pro Val Cys Asn Pro Phe Leu Gly Tyr Cys Gly Ile Pro Asn
1 5 10 15

<210> SEQ ID NO 181
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 181

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Ser Lys Pro Thr Cys Asn Val Phe Asn Ser Trp Cys Ser Val Pro Leu
1 5 10 15

<210> SEQ ID NO 182
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 182

Arg Pro Pro Ala Cys Asn Leu Phe Leu Ser Trp Cys Ser Tyr Asp Ser
1 5 10 15

<210> SEQ ID NO 183
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 183

Gly Arg Ser Val Cys Asn Pro Tyr Lys Ser Trp Cys Pro Val Arg Gln
1 5 10 15

<210> SEQ ID NO 184
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 184

Ala Ser Ser Cys Lys Asp Ser Pro His Phe Arg Cys Leu Phe Pro Leu
1 5 10 15

<210> SEQ ID NO 185
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 185

Leu Ala Asn Cys Pro Asn Ser Pro Gly Phe Leu Cys Leu His Ala Val
1 5 10 15

<210> SEQ ID NO 186
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 186

Pro Phe Ala Cys Pro His Ser Ser Gly Phe Arg Cys Leu Tyr Asn Ile
1 5 10 15

<210> SEQ ID NO 187

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<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 187

Ser Phe Thr Cys Ser Leu Phe Pro Ser Pro His Cys Thr Thr Leu Arg
1 5 10 15

<210> SEQ ID NO 188
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 188

Leu Arg Leu Cys Thr Tyr Gly Gly Gly Lys Tyr Asp Cys Ser Ser Thr
1 5 10 15

<210> SEQ ID NO 189
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 189

Gly Ser Tyr Cys Gln Tyr Arg Pro Phe Ser Ser Phe Cys Asn Arg Ser
1 5 10 15

<210> SEQ ID NO 190
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 190

Cys Ser Tyr Asn Gln Val Leu Gly Arg Ala Cys
1 5 10

<210> SEQ ID NO 191
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 191

Pro His Cys Arg Gln His Pro Leu Asp Arg Trp Met Cys Ser Pro Ser
1 5 10 15

<210> SEQ ID NO 192
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 192

Ser Leu Cys Ser Met Phe Gly Asp Thr Pro His Trp Asn Cys Val Pro
1 5 10 15

<210> SEQ ID NO 193

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 193

Ser Ser Cys Ser Leu Phe Asn Asn Thr Arg His Trp Ser Cys Thr Asp
1 5 10 15

<210> SEQ ID NO 194

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 194

Thr Thr Ala Tyr Pro Asp Cys Phe Trp Cys Ser Leu Phe Gly Pro Pro
1 5 10 15

<210> SEQ ID NO 195

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 195

Met Leu Asp Thr Thr Ile Cys Pro Trp Cys Ser Leu Phe Gly Pro Val
1 5 10 15

<210> SEQ ID NO 196

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (3)..(3)

<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 196

Met Leu Xaa Thr Thr Ile Cys Pro Trp Cys Ser Leu Phe Gly Pro Val
1 5 10 15

<210> SEQ ID NO 197

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 197

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Glu Leu Leu Leu Glu Arg Cys Ser Trp Cys Ser Leu Phe Gly Pro Pro
1 5 10 15

<210> SEQ ID NO 198
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 198

Ser Leu Ser Gln Gln Ser Cys Asp Trp Cys Trp Leu Phe Gly Pro Pro
1 5 10 15

<210> SEQ ID NO 199
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 199

Lys Arg Leu Leu Glu Cys Gly Ala Leu Cys Ala Leu Phe Gly Pro Pro
1 5 10 15

<210> SEQ ID NO 200
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 200

His Thr Ile Leu Thr Cys Asp Ser Gly Phe Cys Thr Leu Phe Gly Pro
1 5 10 15

<210> SEQ ID NO 201
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 201

Asn Leu Trp His Val Cys His Thr Ser Leu Cys His Ser Arg Leu Ala
1 5 10 15

<210> SEQ ID NO 202
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 202

Asn Ser Phe Tyr Leu Cys His Ser Ser Val Cys Gly Gln Leu Pro Ser
1 5 10 15

<210> SEQ ID NO 203

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<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 203

Ala Gly Phe Ser Cys Glu Asn Tyr Phe Phe Cys Pro Pro Lys Asn Leu
1 5 10 15

<210> SEQ ID NO 204
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 204

Ser Trp Cys Thr Val Phe Gly Asn His Asp Pro Ser Cys Asn Ser Arg
1 5 10 15

<210> SEQ ID NO 205
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 205

Cys Ser Ser Asn Gly Arg Trp Lys Ala His Cys
1 5 10

<210> SEQ ID NO 206
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 206

Leu Pro Asn Met Trp Arg Val Val Val Pro Asp Val Tyr Asp Arg Arg
1 5 10 15

<210> SEQ ID NO 207
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 207

Lys His Tyr Cys Phe Gly Pro Lys Ser Trp Thr Thr Cys Ala Arg Gly
1 5 10 15

<210> SEQ ID NO 208
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 208

Pro Trp Cys His Leu Cys Pro Gly Ser Pro Ser Arg Cys Cys Gln Pro
1 5 10 15

<210> SEQ ID NO 209

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 209

Pro Glu Ser Lys Leu Ile Ser Glu Glu Asp Leu Asn Gly Asp Val Ser
1 5 10 15

<210> SEQ ID NO 210

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 210

Ile Trp Asp Arg Val Cys Arg Met Asn Thr Cys His Gln His Ser His
1 5 10 15

<210> SEQ ID NO 211

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 211

Pro Tyr Thr Ile Phe Cys Leu His Ser Ser Cys Arg Ser Ser Ser Ser
1 5 10 15

<210> SEQ ID NO 212

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 212

Asp Trp Cys Leu Thr Gly Pro Asn Thr Leu Ser Phe Cys Pro Arg Arg
1 5 10 15

<210> SEQ ID NO 213

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 213

Leu Ser Thr Trp Arg Cys Leu His Asp Val Cys Trp Pro Pro Leu Lys
1 5 10 15

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<210> SEQ ID NO 214
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 214

Val Tyr Leu Thr Gln Cys Gly Ala Gln Leu Cys Leu Lys Arg Thr Asn
1 5 10 15

<210> SEQ ID NO 215
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 215

Pro Tyr Leu Thr Ser Cys Gly Asp Arg Val Cys Leu Lys Arg Pro Pro
1 5 10 15

<210> SEQ ID NO 216
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 216

Pro Tyr Leu Ser Arg Cys Gly Gly Arg Ile Cys Met His Asp Arg Leu
1 5 10 15

<210> SEQ ID NO 217
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 217

Leu Lys Leu Thr Pro Cys Ser His Gly Val Cys Met His Arg Leu Arg
1 5 10 15

<210> SEQ ID NO 218
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 218

Tyr Tyr Leu Thr Asn Cys Pro Lys Gly His Cys Leu Arg Arg Val Asp
1 5 10 15

<210> SEQ ID NO 219
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 219

Leu Tyr Leu His Ser Cys Ser Arg Gly Ile Cys Leu Ser Pro Arg Val
1 5 10 15

<210> SEQ ID NO 220

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 220

Phe Ser Cys Gln Ser Ser Phe Pro Gly Arg Arg Met Cys Glu Leu Arg
1 5 10 15

<210> SEQ ID NO 221

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 221

His Arg Cys Ser Ala His Gly Ser Ser Ser Ser Phe Cys Pro Gly Ser
1 5 10 15

<210> SEQ ID NO 222

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 222

Lys Thr Trp Asp Cys Arg Asn Ser Gly His Cys Val Ile Thr Phe Lys
1 5 10 15

<210> SEQ ID NO 223

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 223

Ala Thr Trp Asp Cys Arg Asp His Asn Phe Ser Cys Val Arg Leu Ser
1 5 10 15

<210> SEQ ID NO 224

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 224

Leu Arg Cys Trp Gly Met Leu Cys Tyr Ala

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<210> SEQ ID NO 225
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 225

Leu Arg Cys Ile Gly Gln Ile Cys Trp Arg
1 5 10

<210> SEQ ID NO 226
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 226

Leu Lys Cys Leu Tyr Asn Ile Cys Trp Val
1 5 10

<210> SEQ ID NO 227
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 227

Leu Phe Cys Trp Gly Asn Val Cys His Phe
1 5 10

<210> SEQ ID NO 228
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 228

Leu Thr Cys Trp Gly Gln Val Cys Phe Arg
1 5 10

<210> SEQ ID NO 229
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 229

Arg Pro Gly Met Ala Cys Ser Gly Gln Leu Cys Trp Leu Asn Ser Pro
1 5 10 15

<210> SEQ ID NO 230
<211> LENGTH: 16
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 230

Pro His Ala Leu Gln Cys Tyr Gly Ser Leu Cys Trp Pro Ser His Leu
1 5 10 15

<210> SEQ ID NO 231
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 231

Arg Ala Gly Ile Thr Cys His Gly His Leu Cys Trp Pro Ile Thr Asp
1 5 10 15

<210> SEQ ID NO 232
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 232

Arg Pro Ala Leu Lys Cys Ile Gly Thr Leu Cys Ser Leu Ala Asn Pro
1 5 10 15

<210> SEQ ID NO 233
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 233

Pro His Gly Leu Trp Cys His Gly Ser Leu Cys His Tyr Pro Leu Ala
1 5 10 15

<210> SEQ ID NO 234
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 234

Pro His Gly Leu Ile Cys Ala Gly Ser Ile Cys Phe Trp Pro Pro Pro
1 5 10 15

<210> SEQ ID NO 235
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 235

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Pro Arg Asn Leu Thr Cys Tyr Gly Gln Ile Cys Phe Gln Ser Gln His
1 5 10 15

<210> SEQ ID NO 236
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 236

Pro His Asn Leu Ala Cys Gln Asn Ser Ile Cys Val Arg Leu Pro Arg
1 5 10 15

<210> SEQ ID NO 237
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 237

Pro His Gly Leu Thr Cys Thr Asn Gln Ile Cys Phe Tyr Gly Asn Thr
1 5 10 15

<210> SEQ ID NO 238
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 238

His Ser Leu Thr Cys Tyr Gly Gln Ile Cys Trp Val Ser Asn Ile
1 5 10 15

<210> SEQ ID NO 239
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 239

Pro Thr Leu Thr Cys Tyr Asn Gln Val Cys Trp Val Asn Arg Thr
1 5 10 15

<210> SEQ ID NO 240
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 240

Pro Ala Leu Arg Cys Leu Gly Gln Leu Cys Trp Val Thr Pro Thr
1 5 10 15

<210> SEQ ID NO 241

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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 241

Pro Gly Leu Arg Cys Leu Gly Thr Leu Cys Trp Val Pro Asn Arg
1 5 10 15

<210> SEQ ID NO 242
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 242

Arg Asn Leu Thr Cys Trp Asn Thr Val Cys Tyr Ala Tyr Pro Asn
1 5 10 15

<210> SEQ ID NO 243
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 243

Arg Gly Leu Lys Cys Leu Gly Gln Leu Cys Trp Val Ser Ser Asn
1 5 10 15

<210> SEQ ID NO 244
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 244

Pro Thr Leu Lys Cys Ser Gly Gln Ile Cys Trp Val Pro Pro Pro
1 5 10 15

<210> SEQ ID NO 245
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 245

Arg Asn Leu Glu Cys Leu Gly Asn Val Cys Ser Leu Leu Asn Gln
1 5 10 15

<210> SEQ ID NO 246
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 246

Pro	Thr	Leu	Thr	Cys	Leu	Asn	Asn	Leu	Cys	Trp	Val	Pro	Pro	Gln
1				5					10					15

<210> SEQ ID NO 247

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 247

Arg	Gly	Leu	Lys	Cys	Ser	Gly	His	Leu	Cys	Trp	Val	Thr	Pro	Gln
1				5					10					15

<210> SEQ ID NO 248

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 248

His	Gly	Leu	Thr	Cys	His	Asn	Thr	Val	Cys	Trp	Val	His	His	Pro
1				5					10					15

<210> SEQ ID NO 249

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 249

His	Thr	Leu	Glu	Cys	Leu	Gly	Asn	Ile	Cys	Trp	Val	Ile	Asn	Gln
1				5					10					15

<210> SEQ ID NO 250

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 250

His	Gly	Leu	Thr	Cys	Tyr	Asn	Gln	Ile	Cys	Trp	Ala	Pro	Arg	Pro
1				5					10					15

<210> SEQ ID NO 251

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 251

His	Gly	Leu	Ala	Cys	Tyr	Asn	Gln	Leu	Cys	Trp	Val	Asn	Pro	His
1				5					10					15

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<210> SEQ ID NO 252
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 252

Arg Gly Leu Ala Cys Gln Gly Asn Ile Cys Trp Arg Leu Asn Pro
1 5 10 15

<210> SEQ ID NO 253
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 253

Arg Ala Ile Thr Cys Leu Gly Thr Leu Cys Trp Pro Thr Ser Pro
1 5 10 15

<210> SEQ ID NO 254
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 254

Leu Thr Leu Glu Cys Ile Gly Asn Ile Cys Tyr Val Pro His His
1 5 10 15

<210> SEQ ID NO 255
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 255

caggcagcgg gcccgctctgg cccgtgyttt acttgtaga atcattggtg tcct 54

<210> SEQ ID NO 256
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(29)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 256

caggcagcgg gcccgctctgg cccgtgynnk ttacttgta cgaatcattg gtgtcct 57

<210> SEQ ID NO 257
<211> LENGTH: 60
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(29)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(32)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 257

caggcagcgg gcccgctctgg cccgtgynnk nnktttactt gtacgaatca ttggtgtcct 60

<210> SEQ ID NO 258
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 258

caggcagcgg gcccgctctgg cccgtgynht nhtnhtttta cttgtacgaa tcattggtgt 60

cct 63

<210> SEQ ID NO 259
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 259

caggcagcgg gcccgctctgg cccgtgynht nhtnhtnhtt ttactgtac gaatcattgg 60

tgtcct 66

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<210> SEQ ID NO 260
<211> LENGTH: 68
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 260

caggcagcgg gcccgctctgg cccgtgykmt kmtkmtkmtk mttttacttg tacgaatcat 60
tggtgtcc 68

<210> SEQ ID NO 261
<211> LENGTH: 49
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 261

accggaacca ccagactggc crcacgaagg acaccaatga ttcgtacaa 49

<210> SEQ ID NO 262
<211> LENGTH: 52
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (26)..(27)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 262

accggaacca ccagactggc crcamnncca aggacaccaa tgattcgtac aa 52

<210> SEQ ID NO 263
<211> LENGTH: 55
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (26)..(27)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (29)..(30)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 263

accggaacca ccagactggc crcamnnmn cgaaggacac caatgattcg taaaa 55

<210> SEQ ID NO 264
<211> LENGTH: 58
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (27)..(27)

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<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 264

accggaacca ccagactggc crcaadnadm adncgaagga caccaatgat tcgtacaa      58

<210> SEQ ID NO 265
<211> LENGTH: 61
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (27)..(27)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 265

accggaacca ccagactggc crcaadnadm adnadncgaa ggacaccaat gattcgtaca      60
a                                                                    61

<210> SEQ ID NO 266
<211> LENGTH: 64
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide

<400> SEQUENCE: 266

accggaacca ccagactggc crcaakmakm akmakmakmc gaaggacacc aatgattcgt      60
acaa                                                                    64

<210> SEQ ID NO 267
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

Cys Gly Trp Cys
1

<210> SEQ ID NO 268
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 268

Pro Ser Gly Pro Ser Cys His Thr Thr Asn His Trp Pro Ile Ser Ala
1 5 10 15

Val Thr Cys Pro Pro
20

<210> SEQ ID NO 269

<211> LENGTH: 32

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 269

Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
1 5 10 15

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Gly Gly
20 25 30

<210> SEQ ID NO 270

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

Gly Gly Ser Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
1 5 10

<210> SEQ ID NO 271

<211> LENGTH: 33

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 271

Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly Pro Gly Gly Gly Gly Gly
1 5 10 15

Pro Gly Gly Gly Gly Pro Gly Gly Gly Gly Gly Pro Gly Gly Gly Gly
20 25 30

Pro

<210> SEQ ID NO 272

<211> LENGTH: 864

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(864)

<400> SEQUENCE: 272

ggt agt ggt ggt gaa gga ggt tct ggt gga gaa gga ggt agt gga ggt
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
1 5 10 15

48

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gaa ggt gga tcc gga gga gaa gga ggt agt gga ggt gaa gga gga tcc Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser 20 25 30	96
gga gga gaa gga ggt agt ggt ggt gaa gga ggt tct ggt gga gaa gga Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly 35 40 45	144
ggt agt gga ggt gaa ggt gga tcc gga gga gaa gga ggt agt gga ggt Gly Ser Gly Gly Glu Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly 50 55 60	192
gaa gga gga tcc gga gga gaa gga ggt agt gga ggt gaa ggt gga tcc Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser 65 70 75 80	240
ggt gga gaa gga ggt agt gga ggt gaa gga ggt tcc ggt gga gaa gga Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly 85 90 95	288
ggt agt gga gga gag ggt gga tct gga gga gaa gga ggt agt gga gga Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly 100 105 110	336
gag ggt ggt tct gga gga gaa gga ggt agt ggt gga gag ggt gga tct Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser 115 120 125	384
ggt gga gaa gga ggt agt gga gga gaa ggt ggt tct gga gga gaa gga Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly 130 135 140	432
ggt agt ggt ggt gaa gga ggt tct ggt gga gaa gga ggt agt gga ggt Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly 145 150 155 160	480
gaa ggt gga tcc gga gga gaa gga ggt agt gga ggt gaa gga gga tcc Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser 165 170 175	528
gga gga gaa gga ggt agt ggt ggt gaa gga ggt tct ggt gga gaa gga Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly 180 185 190	576
ggt agt gga ggt gaa ggt gga tcc gga gga gaa gga ggt agt gga ggt Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly 195 200 205	624
gaa gga gga tcc gga gga gaa gga ggt agt gga ggt gaa ggt gga tcc Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser 210 215 220	672
ggt gga gaa gga ggt agt gga ggt gaa gga ggt tcc ggt gga gaa gga Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly 225 230 235 240	720
ggt agt gga gga gag ggt gga tct gga gga gaa gga ggt agt gga gga Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly 245 250 255	768
gag ggt ggt tct gga gga gaa gga ggt agt ggt gga gag ggt gga tct Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser 260 265 270	816
ggt gga gaa gga ggt agt gga gga gaa ggt ggt tct gga gga gaa gga Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly 275 280 285	864

<210> SEQ ID NO 273

<211> LENGTH: 288

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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construct
<400> SEQUENCE: 273

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
1      5      10     15
Glu Gly Gly Ser Gly Gly Glu Gly Ser Gly Gly Glu Gly Gly Ser
20     25     30
Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
35     40     45
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
50     55     60
Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
65     70     75     80
Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
85     90     95
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
100    105   110
Glu Gly Gly Ser Gly Gly Glu Gly Ser Gly Gly Glu Gly Gly Ser
115    120   125
Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
130    135   140
Gly Ser Gly Gly Glu Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
145    150   155   160
Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
165    170   175
Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
180    185   190
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
195    200   205
Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
210    215   220
Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
225    230   235   240
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly
245    250   255
Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
260    265   270
Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
275    280   285

<210> SEQ ID NO 274
<211> LENGTH: 864
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
construct
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(864)

<400> SEQUENCE: 274

ggt agt ggt ggt gag ggt gga tcc gga gga agt gga ggt agt ggt gga
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
1      5      10     15

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gaa gga gga tct ggt gga agt gga ggt agt gga ggt gag gga gga tct Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser	96
20 25 30	
ggt gga agt gga ggt agt ggt ggt gag ggt ggt tcc gga gga agt gga Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly	144
35 40 45	
ggt agt gga gga gaa ggt ggt tcc ggt gga agt gga ggt agt ggt gga Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly	192
50 55 60	
gag ggt gga tct gga gga agt gga ggt agt ggt ggt gag ggt ggt tcc Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser	240
65 70 75 80	
gga gga agt gga ggt agt gga gga gaa ggt ggt tcc ggt gga agt gga Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly	288
85 90 95	
ggt agt ggt gga gag ggt gga tct gga gga agt gga ggt agt gga gga Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly	336
100 105 110	
gaa gga gga tct gga gga agt gga ggt agt ggt ggt gag gga ggt tcc Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser	384
115 120 125	
ggt gga agt gga ggt agt ggt gga gaa gga ggt tcc gga gga agt gga Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly	432
130 135 140	
ggt agt ggt ggt gag gga gga tct ggt gga agt gga ggt agt gga gga Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly	480
145 150 155 160	
gag gga ggt tct ggt gga agt gga ggt agt ggt ggt gag ggt ggt tcc Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser	528
165 170 175	
ggt gga agt gga ggt agt ggt ggt gaa gga ggt tct gga gga agt gga Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly	576
180 185 190	
ggt agt ggt gga gaa ggt ggt tcc ggt gga agt gga ggt agt gga gga Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly	624
195 200 205	
gaa gga gga tct gga gga agt gga ggt agt ggt ggt gag ggt ggt tcc Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser	672
210 215 220	
gga gga agt gga ggt agt gga gga gaa ggt ggt tcc ggt gga agt gga Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly	720
225 230 235 240	
ggt agt ggt gga gag ggt gga tct gga gga agt gga ggt agt ggt ggt Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly	768
245 250 255	
gaa gga ggt tcc ggt gga agt gga ggt agt gga ggt gaa ggt gga tct Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser	816
260 265 270	
ggt gga agt gga ggt agt gga ggt gag ggt ggt tcc gga gga agt gga Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly	864
275 280 285	

<210> SEQ ID NO 275

<211> LENGTH: 288

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

-continued

<400> SEQUENCE: 275

Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
1 5 10 15
Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
20 25 30
Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
35 40 45
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
50 55 60
Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
65 70 75 80
Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
85 90 95
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
100 105 110
Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
115 120 125
Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
130 135 140
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
145 150 155 160
Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
165 170 175
Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
180 185 190
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
195 200 205
Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
210 215 220
Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
225 230 235 240
Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly
245 250 255
Glu Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser
260 265 270
Gly Gly Ser Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Ser Gly
275 280 285

<210> SEQ ID NO 276

<211> LENGTH: 671

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

Ser Asp Ser Ser Asp Ser Asp Ser Ser Asp Ser Ser Asn Ser Ser Asp
1 5 10 15
Ser Ser Asp Ser Ser Asp Ser Asp Ser Ser Asp Ser Asn Ser Ser Ser
20 25 30
Asp Ser Asp Ser Ser Asp Ser Asp Ser Ser Asp Ser Ser Asp Ser Asp
35 40 45
Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser
50 55 60

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Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Lys	Ser	Asp	Ser	65	70	75	80
Ser	Lys	Ser	Glu	Ser	Asp	Ser	Ser	Asp	Ser	Asp	Ser	Lys	Ser	Asp	Ser	85	90	95	
Ser	Asp	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Asn	Ser	Asp	Ser	Ser	Asp	100	105	110	
Ser	Ser	Asn	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	115	120	125	
Ser	Asp	Ser	Ser	Ser	Ser	Ser	Asp	Ser	Ser	Ser	Ser	Ser	Ser	Asp	Ser	130	135	140	
Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Glu	145	150	155	160
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Asp	Ser	Ser	Asp	Ser	Ser	165	170	175	
Asp	Ser	Ser	Asn	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Ser	Asn	Ser	Ser		180	185	190	
Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	195	200	205	
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	210	215	220	
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Asn	225	230	235	240
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	245	250	255	
Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	260	265	270	
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	275	280	285	
Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	290	295	300	
Ser	Asp	Ser	Asp	Ser	Ser	Asn	Arg	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	305	310	315	320
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	325	330	335	
Ser	Asp	Ser	Ser	Asp	Ser	Asn	Glu	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	340	345	350	
Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	355	360	365	
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Glu	Ser	Ser	370	375	380	
Asn	Ser	Ser	Asp	Asn	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	385	390	395	400
Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asn	Ser	405	410	415	
Gly	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Asn	Ser	Ser	Asp	420	425	430	
Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	435	440	445	
Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asp	Ser	Ser	Asn	Ser	Ser	Asp	Ser	Ser	450	455	460	

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Asp Ser Ser Asp Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asn
465 470 475 480

Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser
485 490 495

Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser
500 505 510

Asp Ser Ser Asp Ser Ser Gly Ser Ser Asp Ser Ser Asp Ser Ser Asp
515 520 525

Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser
530 535 540

Ser Asp Ser Ser Glu Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser
545 550 555 560

Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp
565 570 575

Ser Ser Asp Ser Ser Asp Ser Ser Asn Ser Ser Asp Ser Ser Asp Ser
580 585 590

Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser
595 600 605

Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp
610 615 620

Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asn Glu Ser
625 630 635 640

Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Ser Asn Ser Ser
645 650 655

Asp Ser Ser Asp Ser Ser Asp Ser Ser Asp Ser Thr Ser Asp Ser
660 665 670

<210> SEQ ID NO 277
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 277

Ser Ser Asp Ser Ser Asn
1 5

<210> SEQ ID NO 278
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 278

Arg Ala Asp Ala Arg Ala Asp Ala
1 5

<210> SEQ ID NO 279
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

-continued

<400> SEQUENCE: 279

Arg Ala Arg Ala Arg Ala Arg Ala
1 5

<210> SEQ ID NO 280

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 280

Asp Ala Asp Ala Asp Ala Asp Ala
1 5

<210> SEQ ID NO 281

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 281

His Ala His Ala His Ala His Ala
1 5

<210> SEQ ID NO 282

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (3)..(8)

<223> OTHER INFORMATION: Wobble base to accommodate diversity in pool

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (10)..(12)

<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 282

Cys Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Cys
1 5 10

<210> SEQ ID NO 283

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (2)..(4)

<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (6)..(11)

<223> OTHER INFORMATION: Wobble base to accommodate diversity in pool

<400> SEQUENCE: 283

Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Cys
1 5 10

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<210> SEQ ID NO 284
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(9)
<223> OTHER INFORMATION: Wobble base to accommodate diversity in pool
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 284

Cys Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys
1 5 10

<210> SEQ ID NO 285
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(3)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(10)
<223> OTHER INFORMATION: Wobble base to accommodate diversity in pool
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(13)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 285

Cys Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys
1 5 10

<210> SEQ ID NO 286
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(4)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(11)
<223> OTHER INFORMATION: Wobble base to accommodate diversity in pool
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(15)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 286

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Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Cys
 1 5 10 15

<210> SEQ ID NO 287
 <211> LENGTH: 18
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (2)..(5)
 <223> OTHER INFORMATION: Variable amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (7)..(12)
 <223> OTHER INFORMATION: Wobble base to accommodate diversity in pool
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (14)..(17)
 <223> OTHER INFORMATION: Variable amino acid
 <400> SEQUENCE: 287

Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
 1 5 10 15

Xaa Cys

<210> SEQ ID NO 288
 <211> LENGTH: 20
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (2)..(6)
 <223> OTHER INFORMATION: Variable amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (8)..(13)
 <223> OTHER INFORMATION: Wobble base to accommodate diversity in pool
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (15)..(19)
 <223> OTHER INFORMATION: Variable amino acid
 <400> SEQUENCE: 288

Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa
 1 5 10 15

Xaa Xaa Xaa Cys
 20

<210> SEQ ID NO 289
 <211> LENGTH: 22
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (2)..(7)
 <223> OTHER INFORMATION: Variable amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (9)..(14)
 <223> OTHER INFORMATION: Wobble base to accommodate diversity in pool

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(21)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 289

Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Cys
20

<210> SEQ ID NO 290
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(8)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)..(15)
<223> OTHER INFORMATION: Wobble base to accommodate diversity in pool

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (17)..(23)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 290

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
20

<210> SEQ ID NO 291
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(9)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)..(16)
<223> OTHER INFORMATION: Wobble base to accommodate diversity in pool

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (18)..(25)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 291

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
20 25

<210> SEQ ID NO 292
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 292

gaaagtggcg gcgaaagccg gtctgcccgg cc 32

<210> SEQ ID NO 293
<211> LENGTH: 102
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (19)..(30)
<223> OTHER INFORMATION: a, c, t, g, unknown or other

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (34)..(51)
<223> OTHER INFORMATION: a, c, t, g, unknown or other

<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (55)..(66)
<223> OTHER INFORMATION: a, c, t, g, unknown or other

<400> SEQUENCE: 293

gaaagcggcg gtgaaagcnn nnnnnnnnnn tgcnnnnnnn nnnnnnnnnn ntgtnnnnnn 60
nnnnnnnagct ccggatctgg tggttccagc ggcggtgaaa gc 102

<210> SEQ ID NO 294
<211> LENGTH: 34
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:

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<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (22)..(22)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 294

Glu Ser Gly Gly Glu Ser Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Cys Xaa Xaa Xaa Xaa Ser Ser Gly Ser Gly Gly Ser Ser Gly Gly
 20 25 30

Glu Ser

<210> SEQ ID NO 295
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 oligonucleotide

<400> SEQUENCE: 295

agaccaccaa ggtcgccgcc tctttcg 27

<210> SEQ ID NO 296
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 oligonucleotide

<400> SEQUENCE: 296

gaaagtggcg gcgaccttgg 20

<210> SEQ ID NO 297
<211> LENGTH: 92
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16)..(27)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(48)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

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<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (52)..(63)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 297

tgcggcgggtg aaagcnnnnn nnnnnntgc nnnnnnnnnn nnnnnnnntg tnnnnnnnnn 60
nnngctccgg atctgggtcc agtctggtgg tg 92

<210> SEQ ID NO 298
<211> LENGTH: 28
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(11)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(18)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)..(23)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 298

Gly Ser Ser Gly Gly Glu Ser Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa
1 5 10 15
Xaa Xaa Cys Xaa Xaa Xaa Ser Ser Gly Ser Gly
20 25

<210> SEQ ID NO 299
<211> LENGTH: 84
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (16)..(27)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (31)..(48)
<223> OTHER INFORMATION: a, c, g, t, unknown or other
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (52)..(63)
<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 299

accagatcc ggagcnnnnn nnnnnnnaca nnnnnnnnnn nnnnnnnngc annnnnnnnn 60
nnngctttca ccgccgtgg aacc 84

<210> SEQ ID NO 300
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

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<400> SEQUENCE: 300

cgaggcctag acccaggtca gaccacctg

29

<210> SEQ ID NO 301

<211> LENGTH: 112

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (32)..(34)

<223> OTHER INFORMATION: a, c, t, g, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (38)..(40)

<223> OTHER INFORMATION: a, c, t, g, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (44)..(46)

<223> OTHER INFORMATION: a, c, t, g, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (83)..(85)

<223> OTHER INFORMATION: a, c, t, g, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (89)..(91)

<223> OTHER INFORMATION: a, c, t, g, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (95)..(97)

<223> OTHER INFORMATION: a, c, t, g, unknown or other

<400> SEQUENCE: 301

ggcccgtctg gccgaaagcg gcggtgaaag cnnntgcnnn tgtnnnagct ccggatctgg

60

tggttccggt agcggcggtg gcnntgcnn ntgtnnngct ccggatctgg gt

112

<210> SEQ ID NO 302

<211> LENGTH: 33

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (7)..(7)

<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (9)..(9)

<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (11)..(11)

<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (24)..(24)

<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (26)..(26)

<223> OTHER INFORMATION: Variable amino acid

<220> FEATURE:

<221> NAME/KEY: MOD_RES

<222> LOCATION: (28)..(28)

<223> OTHER INFORMATION: Variable amino acid

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<400> SEQUENCE: 302

Glu Ser Gly Gly Glu Ser Xaa Cys Xaa Cys Xaa Ser Ser Gly Ser Gly
1 5 10 15

Gly Ser Ser Gly Gly Glu Ser Xaa Cys Xaa Cys Xaa Ser Ser Gly Ser
20 25 30

Gly

<210> SEQ ID NO 303

<211> LENGTH: 124

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (28)..(30)

<223> OTHER INFORMATION: a, c, g, t, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (34)..(36)

<223> OTHER INFORMATION: a, c, g, t, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (40)..(42)

<223> OTHER INFORMATION: a, c, g, t, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (79)..(81)

<223> OTHER INFORMATION: a, c, g, t, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (85)..(87)

<223> OTHER INFORMATION: a, c, g, t, unknown or other

<220> FEATURE:

<221> NAME/KEY: modified_base

<222> LOCATION: (91)..(93)

<223> OTHER INFORMATION: a, c, g, t, unknown or other

<400> SEQUENCE: 303

ccaccagact ggaccagat ccggagcnnn acannngcan nngctaccgc cgctaccgga 60

accaccagat ccggagctnn nacannngca nnngetttca ccgccgcttt cggccagacg 120

ggcc 124

<210> SEQ ID NO 304

<211> LENGTH: 230

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 304

Met Asp Tyr Lys Asp Asp Asp Lys Gly Ser Pro Gly Ser Gly Gly
1 5 10 15

Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser
20 25 30

Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
35 40 45

Gly Ser His Thr Leu Glu Cys Leu Gly Asn Ile Cys Trp Val Ile Asn
50 55 60

Gln Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu
65 70 75 80

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Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
 85 90 95
 Gly Glu Gly Gly Ser His Thr Leu Glu Cys Leu Gly Asn Ile Cys Trp
 100 105 110
 Val Ile Asn Gln Gly Gly Glu Gly Ser Gly Gly Glu Gly Gly Ser
 115 120 125
 Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly
 130 135 140
 Gly Ser Gly Gly Glu Gly Gly Ser His Thr Leu Glu Cys Leu Gly Asn
 145 150 155 160
 Ile Cys Trp Val Ile Asn Gln Gly Gly Glu Gly Gly Ser Gly Gly Glu
 165 170 175
 Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
 180 185 190
 Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser His Thr Leu Glu Cys
 195 200 205
 Leu Gly Asn Ile Cys Trp Val Ile Asn Gln Ser Ser Leu Glu Gly Thr
 210 215 220
 His His His His His His
 225 230

<210> SEQ ID NO 305
 <211> LENGTH: 31
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 peptide

<400> SEQUENCE: 305

Gly Gly Glu Ser Gly Gly Glu Ser His Thr Leu Glu Cys Leu Gly Asn
 1 5 10 15
 Ile Cys Trp Val Ile Asn Gln Ser Ser Gly Ser Gly Gly Ser Gly
 20 25 30

<210> SEQ ID NO 306
 <211> LENGTH: 48
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 peptide
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (2)..(4)
 <223> OTHER INFORMATION: Variable amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (6)..(11)
 <223> OTHER INFORMATION: Variable amino acid
 <220> FEATURE:
 <221> NAME/KEY: MOD_RES
 <222> LOCATION: (13)..(15)
 <223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 306

Ser Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Gly
 1 5 10 15
 Ser Gly Gly Glu Ser Gly Gly Glu Ser His Thr Leu Glu Cys Leu Gly
 20 25 30

-continued

Asn Ile Cys Trp Val Ile Asn Gln Ser Ser Gly Ser Gly Gly Ser Gly
35 40 45

<210> SEQ ID NO 307
<211> LENGTH: 51
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(36)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (38)..(43)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (45)..(47)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 307

Gly Gly Glu Ser Gly Gly Glu Ser His Thr Leu Glu Cys Leu Gly Asn
1 5 10 15

Ile Cys Trp Val Ile Asn Gln Ser Ser Gly Ser Gly Gly Ser Gly Gly
20 25 30

Ser Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Gly
35 40 45

Ser Gly Ser
50

<210> SEQ ID NO 308
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(4)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(11)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(15)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 308

Ser Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Gly
1 5 10 15

Ser Gly Gly Glu Ser Gly Gly Glu Ser His Thr Leu Glu Cys Leu Gly
20 25 30

Asn Ile Cys Trp Val Ile Asn Gln Ser Ser Gly Ser
35 40

<210> SEQ ID NO 309
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(9)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)..(16)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (18)..(20)
<223> OTHER INFORMATION: Variable amino acid

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<400> SEQUENCE: 309

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Gly Gly Ser Gly Gly Ser Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa
1           5           10           15

```

```

Cys Xaa Xaa Xaa Gly Ser Gly Ser
20

```

```

<210> SEQ ID NO 310
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Laticauda semifasciata

```

```

<400> SEQUENCE: 310

```

```

Cys Phe Asn His Gln Ser Gln Pro Gln Thr Thr Lys Thr Cys Ser Pro
1           5           10           15

```

```

Gly Glu Ser Ser Cys Tyr Asn Lys Gln Trp Ser Asp Phe Arg Gly Thr
20           25           30

```

```

Ile Ile Glu Arg Gly Cys Gly Cys Pro Thr Val Lys Pro Gly Ile Lys
35           40           45

```

```

Leu Ser Cys Cys Glu Ser Glu Val Cys
50           55

```

```

<210> SEQ ID NO 311
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: Micrurus nigrocinctus

```

```

<400> SEQUENCE: 311

```

```

Cys His Asn Gln Gln Ser Gln Pro Pro Thr Ile Lys Thr Cys Ser Glu
1           5           10           15

```

```

Gly Gln Cys Tyr Lys Lys Thr Trp Arg Asp His Arg Gly Thr Ile Ser
20           25           30

```

```

Glu Arg Gly Cys Gly Cys Pro Thr Val Lys Pro Gly Ile His Ile Ser
35           40           45

```

```

Cys Cys Ala Ser Asp Lys Cys
50           55

```

```

<210> SEQ ID NO 312
<211> LENGTH: 56
<212> TYPE: PRT
<213> ORGANISM: Naja haje

```

```

<400> SEQUENCE: 312

```

```

Cys Tyr Lys Gln Arg Ser Gln Phe Pro Ile Thr Thr Val Cys Pro Gly
1           5           10           15

```

```

Glu Lys Asn Cys Tyr Lys Lys Gln Trp Ser Gly His Arg Gly Thr Ile

```



```
<210> SEQ ID NO 316
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Naja mossambica
<400> SEQUENCE: 316
```

-continued

Cys His Asn Gln Met Ser Gln Pro Pro Thr Thr Thr Arg Cys Ser Arg
 1 5 10 15
 Trp Glu Thr Asn Cys Tyr Lys Lys Arg Trp Arg Asp His Arg Gly Tyr
 20 25 30
 Lys Thr Glu Arg Gly Cys Gly Cys Pro Thr Val Lys Lys Gly Ile Gln
 35 40 45
 Leu His Cys Cys Thr Ser Asp Asn Cys
 50 55

<210> SEQ ID NO 317
 <211> LENGTH: 57
 <212> TYPE: PRT
 <213> ORGANISM: Laticauda colubrina

<400> SEQUENCE: 317

Cys Phe Asn Gln Gln Ser Gln Pro Lys Thr Thr Lys Ser Cys Pro Pro
 1 5 10 15
 Gly Glu Asn Ser Cys Tyr Asn Lys Gln Trp Arg Asp His Arg Gly Ser
 20 25 30
 Ile Thr Glu Arg Gly Cys Gly Cys Pro Lys Val Lys Pro Gly Ile Lys
 35 40 45
 Leu Arg Cys Cys Glu Ser Glu Asp Cys
 50 55

<210> SEQ ID NO 318
 <211> LENGTH: 55
 <212> TYPE: PRT
 <213> ORGANISM: Dendroaspis polylepis

<400> SEQUENCE: 318

Cys Tyr Asn His Gln Ser Thr Arg Ala Thr Thr Lys Ser Cys Glu Glu
 1 5 10 15
 Asn Ser Cys Tyr Lys Lys Tyr Trp Arg Asp His Arg Gly Thr Ile Ile
 20 25 30
 Glu Arg Gly Cys Gly Cys Pro Lys Val Lys Pro Gly Val Gly Ile His
 35 40 45
 Cys Cys Gln Ser Asp Lys Cys
 50 55

<210> SEQ ID NO 319
 <211> LENGTH: 53
 <212> TYPE: PRT
 <213> ORGANISM: Dendroaspis jamesoni

<400> SEQUENCE: 319

Cys Tyr Asn His Gln Ser Thr Pro Ala Thr Thr Lys Ser Cys Val Glu
 1 5 10 15
 Asn Ser Cys Tyr Lys Ser Ile Trp Ala Asp His Arg Gly Thr Ile Ile
 20 25 30
 Lys Arg Gly Cys Gly Cys Pro Arg Val Lys Ser Lys Ile Lys Cys Cys
 35 40 45
 Lys Ser Asp Asn Cys
 50

<210> SEQ ID NO 320
 <211> LENGTH: 57
 <212> TYPE: PRT

-continued

<213> ORGANISM: *Oxyuranus scutellatus*

<400> SEQUENCE: 320

```

Cys Tyr Asn Gln Gln Ser Glu Ala Lys Thr Thr Thr Thr Cys Ser Gly
1           5           10           15
Gly Val Ser Ser Cys Tyr Lys Lys Thr Trp Ser Asp Gly Arg Gly Thr
20           25           30
Ile Ile Glu Arg Gly Cys Gly Cys Pro Ser Val Lys Lys Gly Ile Glu
35           40           45
Arg Ile Cys Cys Arg Thr Asp Lys Cys
50           55

```

<210> SEQ ID NO 321

<211> LENGTH: 57

<212> TYPE: PRT

<213> ORGANISM: *Ophiophagus hannah*

<400> SEQUENCE: 321

```

Cys Leu Lys Gln Glu Pro Gln Pro Glu Thr Thr Thr Thr Cys Pro Glu
1           5           10           15
Gly Glu Asp Ala Cys Tyr Asn Leu Phe Trp Ser Asp His Ser Glu Ile
20           25           30
Lys Ile Glu Met Gly Cys Gly Cys Pro Lys Thr Glu Pro Tyr Thr Asn
35           40           45
Leu Tyr Cys Cys Lys Ile Asp Ser Cys
50           55

```

<210> SEQ ID NO 322

<211> LENGTH: 55

<212> TYPE: PRT

<213> ORGANISM: *Dendroaspis angusticeps*

<400> SEQUENCE: 322

```

Cys Tyr Ser His Lys Leu Gln Ala Lys Thr Thr Lys Thr Cys Glu Glu
1           5           10           15
Asn Ser Cys Tyr Lys Arg Ser Leu Pro Lys Ile Pro Leu Ile Ile Ile
20           25           30
Gly Arg Gly Cys Gly Cys Pro Leu Thr Leu Pro Phe Leu Arg Ile Lys
35           40           45
Cys Cys Thr Ser Asp Lys Cys
50           55

```

<210> SEQ ID NO 323

<211> LENGTH: 55

<212> TYPE: PRT

<213> ORGANISM: *Dendroaspis angusticeps*

<400> SEQUENCE: 323

```

Cys Tyr Ser His Lys Thr Gln Pro Ser Ala Thr Ile Thr Cys Glu Glu
1           5           10           15
Lys Thr Cys Tyr Lys Lys Ser Val Arg Lys Leu Pro Ala Ile Val Ala
20           25           30
Gly Arg Gly Cys Gly Cys Pro Ser Lys Glu Met Leu Val Ala Ile His
35           40           45
Cys Cys Arg Ser Asp Lys Cys
50           55

```

-continued

<210> SEQ ID NO 324
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: *Dendroaspis polylepis*

<400> SEQUENCE: 324

Cys Tyr Ile His Lys Ala Leu Pro Arg Ala Thr Lys Thr Cys Val Glu
1 5 10 15

Asn Thr Cys Tyr Lys Met Phe Ile Arg Thr Gln Arg Glu Tyr Ile Ser
20 25 30

Glu Arg Gly Cys Gly Cys Pro Thr Ala Met Trp Pro Tyr Gln Thr Glu
35 40 45

Cys Cys Lys Gly Asp Arg Cys
50 55

<210> SEQ ID NO 325
<211> LENGTH: 55
<212> TYPE: PRT
<213> ORGANISM: *Dendroaspis jamesoni*

<400> SEQUENCE: 325

Cys Tyr Thr His Lys Ser Gln Ala Lys Thr Thr Lys Ser Cys Glu Gly
1 5 10 15

Asn Thr Cys Tyr Lys Met Phe Ile Arg Thr Ser Arg Glu Tyr Ile Ser
20 25 30

Glu Arg Gly Cys Gly Cys Pro Thr Ala Met Trp Pro Tyr Gln Thr Glu
35 40 45

Cys Cys Lys Gly Asp Arg Cys
50 55

<210> SEQ ID NO 326
<211> LENGTH: 62
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: His, Ile, Lys, Leu, Asn, Pro, Gln, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Ala, Asp, Glu, Gly, His, Lys, Asn, Pro, Gln, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Lys, Pro, Gln, Arg, Thr, Ala, Asp, Ser or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Ala, Asp, Gly, Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: His, Lys, Asn, Pro, Gln, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Ala or Pro
<220> FEATURE:

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```
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Ile, Lys, Leu, Pro, Gln, Arg or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Ala, Asp, Glu, Gly, Ile, Lys, Asn, Arg, Ser,
Thr
or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: Gly, Ile, Leu, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Ala, Asp, Gly, His, Pro or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ala, Gly, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Ile, Leu, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Pro or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Ala, Glu or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Glu, Gly, Lys, Arg, Phe, Ile, Asn, Ser, Thr
or Tyr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: Glu, Gly, Ile, Lys, Arg or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Ala, Ile, Leu, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: Asp, Glu, Gly, Ile, Lys, Asn, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Leu, Met or Arg

<400> SEQUENCE: 326

Ser Cys His Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ala Val Thr Cys Pro
1          5          10          15

Pro Gly Glu Asn Leu Cys Tyr Arg Lys Met Trp Xaa Xaa Xaa Xaa Xaa
20          25          30

Xaa Xaa Xaa Xaa Xaa Xaa Gly Cys Ala Ala Thr Cys Pro Ser Val Lys
35          40          45

Pro Tyr Glu Glu Val Thr Cys Cys Ser Thr Asp Lys Cys Gly
50          55          60

<210> SEQ ID NO 327
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327
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Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro Phe
 1 5 10 15
 Val Gln Cys Gly Trp Cys His Asp Lys Cys Val Arg Ser Glu Glu Cys
 20 25 30
 Leu Ser Gly Thr Trp Thr Gln Gln Ile Cys
 35 40

<210> SEQ ID NO 328
 <211> LENGTH: 42
 <212> TYPE: PRT
 <213> ORGANISM: Rhinolophus ferrumequinum

<400> SEQUENCE: 328

Cys Glu His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro Phe
 1 5 10 15
 Val Gln Cys Gly Trp Cys His Asn Lys Cys Val Arg Ser Glu Glu Cys
 20 25 30
 Pro Ser Gly Val Trp Thr Gln Asp Val Cys
 35 40

<210> SEQ ID NO 329
 <211> LENGTH: 42
 <212> TYPE: PRT
 <213> ORGANISM: Carollia perspicillata

<400> SEQUENCE: 329

Cys Glu His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro Phe
 1 5 10 15
 Val Gln Cys Gly Trp Cys His Asp Lys Cys Val Arg Leu Glu Thr Cys
 20 25 30
 Pro Ser Gly Ala Trp Thr Gln Glu Ile Cys
 35 40

<210> SEQ ID NO 330
 <211> LENGTH: 42
 <212> TYPE: PRT
 <213> ORGANISM: Otolemur garnettii

<400> SEQUENCE: 330

Cys Glu His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro Phe
 1 5 10 15
 Val Gln Cys Gly Trp Cys His Asp Lys Cys Val Arg Ser Glu Glu Cys
 20 25 30
 Pro Ser Gly Ser Trp Thr Gln Glu Thr Cys
 35 40

<210> SEQ ID NO 331
 <211> LENGTH: 42
 <212> TYPE: PRT
 <213> ORGANISM: Sus scrofa

<400> SEQUENCE: 331

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

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35	40
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<210> SEQ ID NO 332
 <211> LENGTH: 42
 <212> TYPE: PRT
 <213> ORGANISM: Canis familiaris
 <400> SEQUENCE: 332

Cys	Glu	His	Phe	Gln	Ser	Cys	Ser	Gln	Cys	Leu	Ser	Ala	Pro	Pro	Phe
1				5				10					15		
Val	Gln	Cys	Gly	Trp	Cys	His	Asp	Arg	Cys	Val	His	Leu	Glu	Glu	Cys
		20					25					30			
Pro	Thr	Gly	Ala	Trp	Thr	Gln	Glu	Val	Cys						
		35				40									

<210> SEQ ID NO 333
 <211> LENGTH: 42
 <212> TYPE: PRT
 <213> ORGANISM: Rattus norvegicus
 <400> SEQUENCE: 333

Cys	Gly	His	Phe	Gln	Ser	Cys	Ser	Gln	Cys	Leu	Ser	Pro	Pro	Tyr	Phe
1				5				10					15		
Ile	Gln	Cys	Gly	Trp	Cys	His	Asn	Arg	Cys	Val	His	Ser	Asn	Glu	Cys
		20					25						30		
Pro	Ser	Gly	Thr	Trp	Thr	Gln	Glu	Ile	Cys						
		35				40									

<210> SEQ ID NO 334
 <211> LENGTH: 42
 <212> TYPE: PRT
 <213> ORGANISM: Gallus gallus
 <400> SEQUENCE: 334

Cys	His	His	Phe	Gln	Ser	Cys	Ser	Gln	Cys	Leu	Leu	Ala	Pro	Ala	Phe
1				5				10					15		
Met	Arg	Cys	Gly	Trp	Cys	Gly	Gln	Gln	Cys	Leu	Arg	Ala	Pro	Glu	Cys
		20					25						30		
Asn	Gly	Gly	Thr	Trp	Thr	Gln	Glu	Thr	Cys						
		35				40									

<210> SEQ ID NO 335
 <211> LENGTH: 42
 <212> TYPE: PRT
 <213> ORGANISM: Takifugu rubripes
 <400> SEQUENCE: 335

Cys	Asp	His	Leu	Thr	Thr	Cys	Thr	Ser	Cys	Leu	Val	Ser	Ser	Arg	Val
1				5				10					15		
Thr	Glu	Cys	Gly	Trp	Cys	Glu	Gly	Arg	Cys	Thr	Arg	Ala	Asn	Gln	Cys
		20					25						30		
Pro	Pro	Ser	Val	Trp	Thr	Gln	Glu	Tyr	Cys						
		35				40									

<210> SEQ ID NO 336
 <211> LENGTH: 41
 <212> TYPE: PRT
 <213> ORGANISM: Takifugu rubripes

-continued

<400> SEQUENCE: 336

Cys Gln His Phe Leu Thr Cys Ala Val Cys Leu Thr Ala Pro Lys Phe
1 5 10 15
Val Gly Cys Gly Trp Cys Ser Gly Val Cys Ser Trp Glu Ser Asp Cys
20 25 30
Asp His His Trp Arg Asn Asp Ser Cys
35 40

<210> SEQ ID NO 337

<211> LENGTH: 41

<212> TYPE: PRT

<213> ORGANISM: Tetraodon nigroviridis

<400> SEQUENCE: 337

Cys Gln His Phe Leu Thr Cys Ala Met Cys Leu Met Ala Pro Gln Phe
1 5 10 15
Met Gly Cys Gly Trp Cys Ser Gly Val Cys Ser Trp Glu Asn Gln Cys
20 25 30
Asp Asp Arg Trp Arg Asn Glu Ser Cys
35 40

<210> SEQ ID NO 338

<211> LENGTH: 41

<212> TYPE: PRT

<213> ORGANISM: Tetraodon nigroviridis

<400> SEQUENCE: 338

Cys Ala His Phe Arg Thr Cys Ser Met Cys Leu Met Ala Pro Arg Phe
1 5 10 15
Met Asn Cys Gly Trp Cys Ser Gly Val Cys Ser Arg Gln His Glu Cys
20 25 30
Thr Ser Trp Gln Thr Ser Ala Ser Cys
35 40

<210> SEQ ID NO 339

<211> LENGTH: 41

<212> TYPE: PRT

<213> ORGANISM: Takifugu rubripes

<400> SEQUENCE: 339

Cys Ala His Phe Arg Thr Cys Ser Met Cys Leu Met Ala Pro Arg Phe
1 5 10 15
Met Asn Cys Gly Trp Cys Ser Gly Val Cys Ser Arg Gln His Gln Cys
20 25 30
Asp Met Gln Trp Glu Lys Asp Ser Cys
35 40

<210> SEQ ID NO 340

<211> LENGTH: 41

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

Cys Arg His Phe Leu Thr Cys Gly Arg Cys Leu Arg Ala Trp His Phe
1 5 10 15
Met Gly Cys Gly Trp Cys Gly Asn Met Cys Gly Gln Gln Lys Glu Cys
20 25 30

-continued

Pro Gly Ser Trp Gln Gln Asp His Cys
35 40

<210> SEQ ID NO 341
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 341

Cys His His Phe Leu Thr Cys Gly Ser Cys Leu Arg Ala Gln Arg Phe
1 5 10 15

Met Gly Cys Gly Trp Cys Gly Gly Met Cys Gly Arg Gln Lys Glu Cys
20 25 30

Pro Gly Ser Trp Gln Gln Asp His Cys
35 40

<210> SEQ ID NO 342
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 342

Cys Arg His Phe Leu Thr Cys Trp Arg Cys Leu Arg Ala Gln Arg Phe
1 5 10 15

Met Gly Cys Gly Trp Cys Gly Asp Arg Cys Asp Arg Gln Lys Glu Cys
20 25 30

Pro Gly Ser Trp Gln Gln Asp His Cys
35 40

<210> SEQ ID NO 343
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Gallus gallus

<400> SEQUENCE: 343

Cys Arg His Phe Ser Thr Cys Asp Arg Cys Leu Arg Ala Glu Arg Phe
1 5 10 15

Met Gly Cys Gly Trp Cys Gly Asn Gly Cys Thr Arg His His Glu Cys
20 25 30

Ala Gly Pro Trp Val Gln Asp Ser Cys
35 40

<210> SEQ ID NO 344
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Asp, Glu, Gly, His, Gln or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Phe or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: His, Ile, Lys, Leu, Asn, Pro, Gln, Arg, Ser or
Thr
<220> FEATURE:

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<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Ala, Gly, Arg, Ser, Thr or Trp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Lys, Leu, Met, Gln or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Gly, Ile, Leu, Met, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Ala or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Ala, Glu, Pro, Gln, Ser or Trp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: Ala, Asp, Glu, Gly, His, Pro, Gln or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Phe or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Ala, Ile, Met, Thr or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Asp, Glu, Gly, His, Lys, Asn, Gln, Arg or Ser

<400> SEQUENCE: 344

Ser Cys Xaa His Xaa Xaa Xaa Cys Xaa Xaa Cys Leu Xaa Xaa Xaa Xaa
1           5           10           15

Xaa Xaa Xaa Cys Gly Trp Cys His Asp Lys Cys Val Arg Ser Glu Glu
20           25           30

Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile Cys Gly
35           40

<210> SEQ ID NO 345
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)..(26)
<223> OTHER INFORMATION: Asp, Gly, His, Asn, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Asp, Gly, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (26)..(26)
<223> OTHER INFORMATION: Glu, Gly, Lys, Met, Arg or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)..(28)
<223> OTHER INFORMATION: Ala, Gly, Ile, Ser, Thr or Val
<220> FEATURE:

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<221> NAME/KEY: MOD_RES
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: His, Gln, Arg or Trp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Ser, Leu, Ala, Asp, Glu, His or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Asp, Glu, His, Lys, Asn or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Asp, Glu, His or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Ala, Asp, His, Asn, Pro or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (35)..(35)
<223> OTHER INFORMATION: Ala, Asp, Gly, Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (36)..(36)
<223> OTHER INFORMATION: Asp, Glu, Gly, His, Lys, Asn, Gln, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: Ala, Phe, Ile, Ser, Thr, Val or not present
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (39)..(39)
<223> OTHER INFORMATION: Gln, Arg or Thr
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (40)..(40)
<223> OTHER INFORMATION: His, Lys, Asn or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Asp, Glu, His or Gln
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: Ala, Asp, Phe, His, Ile, Leu, Asn, Pro, Ser,
    Thr, Val or Tyr

<400> SEQUENCE: 345

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1           5           10           15

Phe Val Gln Cys Gly Trp Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa
20           25           30

Cys Xaa Xaa Xaa Xaa Trp Xaa Xaa Xaa Xaa Cys Gly
35           40

<210> SEQ ID NO 346
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(7)
<223> OTHER INFORMATION: Variable amino acid

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<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (9)..(10)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (13)..(19)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 346

Ser Cys Xaa His Xaa Xaa Xaa Cys Xaa Xaa Cys Leu Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Cys Gly Trp Cys His Asp Lys Cys Val Arg Ser Glu Glu
20 25 30

Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile Cys Gly
35 40

<210> SEQ ID NO 347
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (24)..(26)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (28)..(32)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (34)..(37)
<223> OTHER INFORMATION: Variable amino acid
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (39)..(42)
<223> OTHER INFORMATION: Variable amino acid

<400> SEQUENCE: 347

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1 5 10 15

Phe Val Gln Cys Gly Trp Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa
20 25 30

Cys Xaa Xaa Xaa Xaa Trp Xaa Xaa Xaa Xaa Cys Gly
35 40

<210> SEQ ID NO 348
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 348

Ser Cys His His Phe Ile Ser Cys Gly Arg Cys Leu Arg Ser Trp His
1 5 10 15

Val Val Asp Cys Gly Trp Cys His Asp Lys Cys Val Arg Ser Glu Glu
20 25 30

Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile Cys Gly
35 40

-continued

<210> SEQ ID NO 349
<211> LENGTH: 43
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 349

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1 5 10 15
Phe Val Gln Cys Gly Trp Cys Gly Asp Met Cys Ala Arg Val Gln Gln
20 25 30
Cys His Asp Arg Trp Thr His His Ala Cys Gly
35 40

<210> SEQ ID NO 350
<211> LENGTH: 43
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 350

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1 5 10 15
Phe Val Gln Cys Gly Trp Cys His Asp Lys Cys Gly His Gln Asp Glu
20 25 30
Cys Thr Ala Ser Trp Arg Lys Glu Ala Cys Gly
35 40

<210> SEQ ID NO 351
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 351

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1 5 10 15
Phe Val Gln Cys Gly Trp Cys Arg Asn Met Cys Val Gln Glu Lys Gln
20 25 30
Cys Asp Asp Ser Ile Trp Lys Asn Gln His Cys Gly
35 40

<210> SEQ ID NO 352
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 352

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1 5 10 15
Phe Val Gln Cys Gly Trp Cys Arg Asp Arg Cys Ser Arg Glu Asp His
20 25 30

-continued

Cys Pro Thr Lys Thr Trp Arg Asn His Pro Cys Gly
35 40

<210> SEQ ID NO 353
<211> LENGTH: 43
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 353

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1 5 10 15

Phe Val Gln Cys Gly Trp Cys Asn Asn Val Cys Ser Arg His Asn Asp
20 25 30

Cys Asp Asn Asn Trp Gln His Gln Asn Cys Gly
35 40

<210> SEQ ID NO 354
<211> LENGTH: 43
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 354

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1 5 10 15

Phe Val Gln Cys Gly Trp Cys Asn Ser Met Cys Gly Arg Ala His Asp
20 25 30

Cys Thr Asp His Trp Gln Lys Gln His Cys Gly
35 40

<210> SEQ ID NO 355
<211> LENGTH: 43
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 355

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro
1 5 10 15

Phe Val Gln Cys Gly Trp Cys Gly Asn Met Cys Val Arg Ser Glu Glu
20 25 30

Cys His Thr Asp Trp Arg His Asp Thr Cys Gly
35 40

<210> SEQ ID NO 356
<211> LENGTH: 44
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 356

Ser Cys Arg His Phe Gln Ser Cys Ser Gln Cys Leu Ser Ala Pro Pro

-continued

1	5	10	15
Phe Val Gln Cys Gly Trp Cys Asn Ser Met Cys Gly Arg Ala Gln Asp			
	20	25	30
Cys Asn Asp Arg Thr Trp Lys Gln His Thr Cys Gly			
	35	40	

<210> SEQ ID NO 357
 <211> LENGTH: 51
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 357

Gln Ala Ala Gly Pro Ser Gly Pro Cys Ser Tyr Tyr Ala Tyr Phe Thr			
1	5	10	15
Cys Thr Asn His Trp Cys Pro Ser Pro Phe Ala Phe Thr Cys Thr			
	20	25	30
Asn His Trp Cys Pro Ser Tyr Tyr Asp Ser Ala Tyr Cys Gly Gln Ser			
	35	40	45
Gly Gly Ser			
	50		

<210> SEQ ID NO 358
 <211> LENGTH: 37
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 358

Gln Ala Ala Gly Pro Ser Gly Pro Cys Ala Ala Tyr Ala Tyr Phe Thr			
1	5	10	15
Cys Thr Asn His Trp Cys Pro Ser Tyr Tyr Ser Ala Ala Cys Gly Gln			
	20	25	30
Ser Gly Gly Ser Gly			
	35		

<210> SEQ ID NO 359
 <211> LENGTH: 37
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 359

Gln Ala Ala Gly Pro Ser Gly Pro Cys Ala Tyr Ala Tyr Tyr Phe Thr			
1	5	10	15
Cys Thr Asn His Trp Cys Pro Ser Tyr Tyr Ala Tyr Tyr Cys Gly Gln			
	20	25	30
Ser Gly Gly Ser Gly			
	35		

<210> SEQ ID NO 360
 <211> LENGTH: 37
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 360

Gln Ala Ala Gly Pro Ser Gly Pro Cys Ala Tyr Tyr Ser Tyr Phe Thr
1           5           10           15

Cys Thr Asn His Trp Cys Pro Ser Tyr Tyr Ser Ser Tyr Cys Gly Gln
      20           25           30

Ser Gly Gly Ser Gly
      35

<210> SEQ ID NO 361
<211> LENGTH: 126
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(39)
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (58)..(126)

<400> SEQUENCE: 361

atg gat tat aaa gac gat gac gat aaa ggg tct cca ggt tagtaaccta      49
Met Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser Pro Gly
1           5           10

ggtgatag gga ggt tcg tct tca ctc gag ggt acc cat cac cat cac cat      99
      Gly Gly Ser Ser Ser Leu Glu Gly Thr His His His His His
      15           20           25

cac gag ctc gta ccg gta gaa aaa atg      126
His Glu Leu Val Pro Val Glu Lys Met
      30           35

<210> SEQ ID NO 362
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 362

Met Asp Tyr Lys Asp Asp Asp Asp Lys Gly Ser Pro Gly
1           5           10

<210> SEQ ID NO 363
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 363

Gly Gly Ser Ser Ser Leu Glu Gly Thr His His His His His His Glu
1           5           10           15

Leu Val Pro Val Glu Lys Met
      20

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<210> SEQ ID NO 364
 <211> LENGTH: 463
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 364

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Met Gly His His His His His His Gly Gly Ser Gly Gly Glu Gly Gly
 1          5          10          15
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu
 20          25          30
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Ser Gly
 35          40          45
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly
 50          55          60
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Ser Gly Gly Glu
 65          70          75          80
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
 85          90          95
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly
100          105          110
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu
115          120          125
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
130          135          140
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly
145          150          155          160
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Ser Gly Gly Glu
165          170          175
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
180          185          190
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly
195          200          205
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu
210          215          220
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
225          230          235          240
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly
245          250          255
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu
260          265          270
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
275          280          285
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Cys Asp Leu Pro Gln Thr
290          295          300
His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg
305          310          315          320
Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe
325          330          335
Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro
340          345          350
  
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Val	Leu	His	Glu	Met	Ile	Gln	Gln	Ile	Phe	Asn	Leu	Phe	Ser	Thr	Lys
	355					360						365			
Asp	Ser	Ser	Ala	Ala	Trp	Asp	Glu	Thr	Leu	Leu	Asp	Lys	Phe	Tyr	Thr
	370					375					380				
Glu	Leu	Tyr	Gln	Gln	Leu	Asn	Asp	Leu	Glu	Ala	Cys	Val	Ile	Gln	Gly
385					390					395					400
Val	Gly	Val	Thr	Glu	Thr	Pro	Leu	Met	Lys	Glu	Asp	Ser	Ile	Leu	Ala
			405						410					415	
Val	Arg	Lys	Tyr	Phe	Gln	Arg	Ile	Thr	Leu	Tyr	Leu	Lys	Glu	Lys	Lys
			420					425					430		
Tyr	Ser	Pro	Cys	Ala	Trp	Glu	Val	Val	Arg	Ala	Glu	Ile	Met	Arg	Ser
		435					440					445			
Phe	Ser	Leu	Ser	Thr	Asn	Leu	Gln	Glu	Ser	Leu	Arg	Ser	Lys	Glu	
	450					455					460				

<210> SEQ ID NO 365

<211> LENGTH: 472

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 365

Met	Gly	His	His	His	His	His	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	
1				5				10					15		
Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu
			20				25					30			
Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly
		35					40					45			
Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly
	50					55				60					
Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu
65					70				75						80
Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly
			85					90						95	
Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly
		100					105					110			
Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu
	115					120						125			
Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly
	130					135					140				
Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly
145					150				155						160
Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu
			165					170						175	
Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly
		180						185					190		
Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly
	195						200					205			
Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu
	210					215					220				
Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly	Gly	Glu	Gly	Gly	Ser	Gly
225					230					235					240

-continued

Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly
 245 250 255
 Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu
 260 265 270
 Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
 275 280 285
 Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Thr Pro Leu Gly Pro Ala
 290 295 300
 Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg
 305 310 315 320
 Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr
 325 330 335
 Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu
 340 345 350
 Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln
 355 360 365
 Leu Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln
 370 375 380
 Gly Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr
 385 390 395 400
 Leu Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp
 405 410 415
 Gln Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln
 420 425 430
 Gly Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly
 435 440 445
 Val Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg
 450 455 460
 Val Leu Arg His Leu Ala Gln Pro
 465 470

<210> SEQ ID NO 366

<211> LENGTH: 489

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic construct

<400> SEQUENCE: 366

Met Gly His His His His His His Gly Gly Ser Gly Gly Glu Gly Gly
 1 5 10 15
 Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu
 20 25 30
 Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
 35 40 45
 Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly
 50 55 60
 Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu
 65 70 75 80
 Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly
 85 90 95
 Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly

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100	105	110
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu		
115	120	125
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly		
130	135	140
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly		
145	150	155
160		
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu		
165	170	175
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly		
180	185	190
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly		
195	200	205
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu		
210	215	220
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly		
225	230	235
240		
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly		
245	250	255
Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu		
260	265	270
Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Ser Gly		
275	280	285
Gly Glu Gly Gly Ser Gly Gly Glu Gly Gly Phe Pro Thr Ile Pro Leu		
290	295	300
Ser Arg Leu Phe Asp Asn Ala Met Leu Arg Ala His Arg Leu His Gln		
305	310	315
320		
Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala Tyr Ile Pro Lys		
325	330	335
Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu Cys Phe		
340	345	350
Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln Lys		
355	360	365
Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp		
370	375	380
Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val		
385	390	395
400		
Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu		
405	410	415
Glu Gly Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg		
420	425	430
Thr Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser		
435	440	445
His Asn Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe		
450	455	460
Arg Lys Asp Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys		
465	470	475
480		
Arg Ser Val Glu Gly Ser Cys Gly Phe		
485		

1-49. (canceled)

50. A biologically active protein comprising at least two domains wherein (a) a first domain of said at least two domains comprises an amino acid sequence having and/or mediating said biological activity; and (b) a second domain of said at least two domains comprises an amino acid sequence consisting preferably of at least about 100 amino acid residues forming random coil conformation whereby said random coil conformation mediates an increased in vivo and/or in vitro stability of said biologically active protein.

51. The biologically active protein according to claim **50**, wherein said second domain forming random coil conformation consists of alanine, serine and proline residues.

52. The biologically active protein according to claim **50** or **51**, wherein said second domain forming random coil conformation comprises a plurality of amino acid repeats, wherein said repeat consist of Ala, Ser, and Pro residues and wherein no more than 6 consecutive amino acid residues are identical.

53. The biologically active protein according to any one of claims **50-52**, wherein said proline residues constitute more than 4% and less than 40% of the amino acids of said second domain forming random coil conformation.

54. The biologically active protein according to any one of claims **50-53**, wherein said second domain of said at least two domains comprises an amino acid sequence consisting of about 100 to 3000 amino acid residues forming random coil conformation.

55. The biologically active protein according to any one of claims **50-54**, wherein said polypeptide with biological activity is selected from the group consisting of binding molecules, antibody fragments, cytokines, growth factors, hormones or enzymes.

56. The biologically active protein according to claim **55** wherein said binding molecule is selected from the group consisting of antibodies, antibody fragments, domain antibodies and lipocalins.

57. The biologically active protein according to any one of claims **50-56**, wherein said polypeptide with biological activity is selected from the group consisting of granulocyte colony stimulating factor, human growth hormone, alphainterferon, betainterferon, gammainterferon, tumor necrosis factor, erythropoietin, coagulation factor VIII, soluble tumor necrosis factor I and II receptor, interleukin 2 and neutrophil gelatinase associated lipocalin.

58. The biologically active protein according to any one of claims **50-57**, wherein said increased in vivo stability of said biologically active protein is a prolonged plasma half life of said biologically active protein comprising said random coil forming second domain when compared to said biologically active protein lacking said random coil forming second domain.

59. A composition comprising the biologically active protein according to any one of claims **50-58**.

60. The composition according to claim **59** which is a pharmaceutical composition, optionally further comprising a pharmaceutical acceptable carrier.

61. A nucleic acid molecule encoding the biologically active protein of any one of claims **50-58**.

62. A vector comprising the nucleic acid of claim **61**.

63. A cell comprising the nucleic acid according to claim **61** or the vector according to claim **62**.

64. A method for preparing a biologically active protein comprising culturing the cell according to claim **63** and isolating said biologically active protein from the culture.

65. A method of treating a disease condition selected from the group consisting of hormone deficiency related disorders, autoimmune disease, cancer, anaemia, neovascular diseases, infectious/inflammatory diseases, thrombosis, myocardial infarction, diabetes, reperfusion injury, and a kidney disease, comprising administering to a subject in need thereof a composition according to claim **60**.

* * * * *