

HALF-LIFE EXTENDING MOIETIES AND METHODS OF USING THE SAME

[001] The disclosure relates generally to biology and medicine, and more particularly it relates to single domain antibodies known as variable domains of heavy chain-only antibodies (VHH) that are engineered/modified to act as half-life ($t_{1/2}$)-extending moieties for use with therapeutic agents, especially for improving $t_{1/2}$ of biological-based therapeutic agents (*i.e.*, biotherapeutics or biologics). The disclosure further relates to fusions and conjugates that include one or more of the VHH-based $t_{1/2}$ -extending moieties and a therapeutic agent, as well as pharmaceutical compositions including the same and their use in treating various conditions, diseases or disorders.

[002] Biotherapeutics are native or modified components of physiological pathways and tend to be highly selective, efficacious and safe. However, they come with some limitations. One limitation, and with few exceptions, is that biotherapeutics cannot be orally administered. Another limitation is that many biotherapeutics have a relatively short $t_{1/2}$ when used in a clinical setting.

[003] Several strategies exist for extending the $t_{1/2}$ of biotherapeutics, which can improve their pharmacokinetic (PK) and/or pharmacodynamic (PD) profiles. Such strategies typically use bulking moieties or neonatal Fc receptor (FcRn)-mediated recycling. In this manner, antibodies (Abs) or fragments thereof (*e.g.*, Fab, Fc, *etc.*); polymers such as polyethylene glycol (PEG), polysialic acid (PSA), hyaluronic acid (HA) and hydroxy-ethyl-starch (HES); fatty acids and other lipids; N- or O-glycosylation; and serum albumin or other plasma proteins (such as transferrin), can be covalently and/or non-covalently bound to a given biotherapeutic to extend its $t_{1/2}$. See, *e.g.*, Hamers-Casterman *et al.* (1993) *Nature* 363:446-448; Harmsen & Haard (2007) *Appl. Microbiol. Biotechnol.* 77:13-22; Kontermann (2016) *Expert Opin. Biol. Ther.* 16:903-915; Müller *et al.* (2012) *MAbs* 4:673-685; Podust *et al.* (2013) *Protein Eng. Des. Sel.* 26:743-753; Strohl (2015) *BioDrugs* 29:215-239; and Werle U Bernkop-Schnürch (2006) *Amino Acids* 30:351-367.

[004] Despite the vast number of $t_{1/2}$ -extending strategies, there is a need for additional structures for extending or improving PK properties, such as the $t_{1/2}$, of biotherapeutics.

[004a] In an aspect of the present disclosure, there is provided a compound comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-37 and 124-126, or at least about 90% sequence similarity thereto.

[004b] In another aspect of the present disclosure, there is provided a compound comprising a structure of:

M-X₁,

X₁-M,

M-L₁-X₁,

X₁-L₁-M,

X₁-M-X₂,

X₂-M-X₁,

X₁-L₁-M-X₂,

X₂-L₁-M-X₁,

X₁-M-L₁-X₂,

X₂-M-L₁-X₁,

X₁-L₁-M-L₂-X₂,

X₂-L₁-M-L₂-X₁,

M-L₁-X₁-L₂-X₂,

M-L₁-X₂-L₂-X₁,

X₁-L₂-X₂-L₁-M, or

X₂-L₂-X₁-L₁-M,

wherein M is an amino acid sequence selected from the group consisting of SEQ ID NOS:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 124, 125 and 126, or at least about 90% sequence similarity thereto,

wherein X₁ is a first biotherapeutic,

wherein X₂ (if present) is a second biotherapeutic,

wherein L₁ (if present) is a first linker having an amino acid sequence selected from the group consisting of (GGGGQ)_n (SEQ ID NO:38), (GGGQ)_n (SEQ ID NO:39), (GGGGS)_n (SEQ ID NO:40), (PGPQ)_n (SEQ ID NO:41), (PGPA)_n (SEQ ID NO:42), (GGGG(AP)_nGGGG) (SEQ ID NO:43), (GGE)_n (SEQ ID NO:44), (GGGGGE)_n (SEQ ID NO:45), (GGK)_n (SEQ ID NO:46), (GGGGK)_n (SEQ ID NO:47), (GGGG(EP)_nGGGG)

1b

(SEQ ID NO:48), (GGGG(KP)_nGGGG) (SEQ ID NO:49), (PGPE)_n (SEQ ID NO:50), and (PGPK)_n (SEQ ID NO:51), wherein n can be from 1 to 10, and

wherein L₂ (if present) is a second linker having an amino acid sequence selected from the group consisting of SEQ ID NOS:64 and 65, or at least about 90% sequence similarity thereto.

[004c] In a further aspect of the present disclosure, there is provided a compound comprising any one of SEQ ID NOS:100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117 or 118, or at least about 90% sequence similarity thereto.

[004d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable buffer.

[004e] In a further aspect of the present disclosure, there is provided a compound as disclosed herein for use in therapy.

[004f] In another aspect of the present disclosure, there is provided a compound as disclosed herein for use in treating cardiovascular, neurological, immunological, metabolic, oncological, psychological, pulmonary and/or renal conditions, diseases and/or disorders.

[004g] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for treating cardiovascular, neurological, immunological, metabolic, oncological, psychological, pulmonary and/or renal conditions, diseases and/or disorders.

[005] To address this need, the disclosure first describes compounds that can be used as t_{1/2}-extending moieties for biotherapeutics. In one instance, a compound is provided that

CLAIMS

The invention claimed is:

1. A compound comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1-37 and 124-126, or at least about 90% sequence similarity thereto.

~~2. — The compound of Claim 1, wherein the amino acid sequence is:~~

~~EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKERE FVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:1) or at least about 90% sequence similarity thereto.~~

~~3. — The compound of Claim 1, wherein the amino acid sequence is:~~

~~EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKERE FVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:2) or at least about 90% sequence similarity thereto.~~

~~4. — The compound of Claim 1, wherein the amino acid sequence is:~~

~~EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKERE FVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVAD
LPPYWGQGTLVTVSSPP (SEQ ID NO:3) or at least about 90% sequence similarity
thereto.~~

~~5. — The compound of Claim 1, wherein the amino acid sequence is:~~

~~EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKERE FVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVAD
LPPYWGQGTLVTVSSPP (SEQ ID NO:4) or at least about 90% sequence similarity
thereto.~~

6. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLVESGGGLVQAGGSLRLSCAASGRTVSSTAVAWFRQAPGKEREFVAGIGGSVDITYYLDISKGRFTISKDNTKNTVYLQMNSLRPEDTAVYYCAVRPGRPLITSRDANLYDYWGQGTLVTVSS (SEQ ID NO:5) or at least about 90% sequence similarity thereto.

7. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQPGGSLRLSCAASGRTVSSTAVAWFRQAPGKEREFVAGIGGSVDITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAVRPGRPLITSRDANLYDYWGQGTLVTVSS (SEQ ID NO:6) or at least about 90% sequence similarity thereto.

8. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQPGGSLRLSCAASGRYIDSTAVAWFRQAPGKEREFVAGIGGGVDITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSRVANLYPYWGQGTLVTVSS (SEQ ID NO:7) or at least about 90% sequence similarity to thereto.

9. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQPGGSLRLSCAASYRYIDETAVAWFRQAPGKEREFVAGIGGGVDITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVADLYPYWGQGTLVTVSS (SEQ ID NO:8) or at least about 90% sequence similarity thereto.

10. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQPGGSLRLSCAASGAYIDETAVAWFRQAPGKEREFVAGIGGGVDITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVADLYPYWGQGTLVTVSS (SEQ ID NO:9) or at least about 90% sequence similarity thereto.

11. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQPGGSLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGVDITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVADLYPYWGQGTLVTVSS (SEQ ID NO:10) or at least about 90% sequence similarity thereto.

12. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DQTTYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:11) or at least about 90% sequence similarity thereto.

13. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITAYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:12) or at least about 90% sequence similarity thereto.

14. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITEYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVADL
YPYWGQGTLVTVSS (SEQ ID NO:13) or at least about 90% sequence similarity thereto.

15. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITQYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:14) or at least about 90% sequence similarity thereto.

16. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITSYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVADL
YPYWGQGTLVTVSS (SEQ ID NO:15) or at least about 90% sequence similarity thereto.

17. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITTYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITSKVADL
YPYWGQGTLVTVSS (SEQ ID NO:16) or at least about 90% sequence similarity thereto.

18. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGKPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:17) or at least about 90% sequence similarity thereto.

19. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGQPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:18) or at least about 90% sequence similarity thereto.

20. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGSPLITSKVADL
YPYWGQGTLVTVSS (SEQ ID NO:19) or at least about 90% sequence similarity thereto.

21. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRELITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:20) or at least about 90% sequence similarity thereto.

22. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRQLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:21) or at least about 90% sequence similarity thereto.

23. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRSLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:22) or at least about 90% sequence similarity thereto.

24. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPEITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:23) or at least about 90% sequence similarity thereto.

25. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPGITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:24) or at least about 90% sequence similarity thereto.

26. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPQITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:25) or at least about 90% sequence similarity thereto.

27. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPQTITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:26) or at least about 90% sequence similarity thereto.

28. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKEREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCAARPGRPLITEKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:27) or at least about 90% sequence similarity thereto.

29. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES GGGLVQP GGSRLRLSCAASGRYIDETAVAWFRQAPGKGREFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCATRPGRPLITSKVADL
YPYWGQGTLVTVSS (SEQ ID NO:28) or at least about 90% sequence similarity thereto.

30. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMN~~SLRPEDTAVYYCAARQGRPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:29) or at least about 90% sequence similarity thereto.

31. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMN~~SLRPEDTAVYYCATRQGRPLITSKVAD
LPPYWGQGTLVTVSS (SEQ ID NO:30) or at least about 90% sequence similarity thereto.

32. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMN~~SLRPEDTAVYYCAARPGRPLITSQVAD
LPPYWGQGTLVTVSS (SEQ ID NO:31) or at least about 90% sequence similarity thereto.

33. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMN~~SLRPEDTAVYYCAARPGRPLITSKQAD
LPPYWGQGTLVTVSS (SEQ ID NO:32) or at least about 90% sequence similarity thereto.

34. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMN~~SLRPEDTAVYYCAARPGRPLITSKVAEL
YPYWGQGTLVTVSS (SEQ ID NO:33) or at least about 90% sequence similarity thereto.

35. — The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMN~~SLRPEDTAVYYCAARPGRPLITSKVASL
YPYWGQGTLVTVSS (SEQ ID NO:34) or at least about 90% sequence similarity thereto.

36. —The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMNSLRPEDTAVYYCAAR~~PGRPLITSKQAE~~L~~
YPYWGQGTLVTVSS (SEQ ID NO:35) or at least about 90% sequence similarity thereto.

37. —The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMNSLRPEDTAVYYCAAR~~PGRPLITSKQAS~~L~~
YPYWGQGTLVTVSS (SEQ ID NO:36) or at least about 90% sequence similarity thereto.

38. —The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMNSLRPEDTAVYYCAAR~~PGRPLITSK~~VAD~~
L~~YPYWGQGTLVTVSS~~C (SEQ ID NO:37) or at least about 90% sequence similarity
thereto.

39. —The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMNSLRPEDTAVYYCGAR~~PGRPLITSK~~VAD~~
L~~YPYWGQGTLVTVSS~~C (SEQ ID NO:124) or at least about 90% sequence similarity
thereto.

40. —The compound of Claim 1, wherein the amino acid sequence is:

EVQLLES~~GGGLVQPGGSLRL~~SCAASGRYIDETAVAWFRQAPGK~~GREFVAGIGGGV~~
DITYYADSVKGRFTISRDN~~SKNTLYLQMNSLRPEDTAVYYCGAR~~PGRPLITSK~~VAD~~
L~~YPYWGQGTLVTVSS~~PP (SEQ ID NO:125) or at least about 90% sequence similarity
thereto.

41. —The compound of Claim 1, wherein the amino acid sequence is:

~~EVQLLES GGG LVQP GGS LRLSCAASGRYIDETAVAWFRQAPGKGRFVAGIGGGV
DITYYADSVKGRFTISRDN SKNTLYLQMNSLRPEDTAVYYCGTRPGRPLITSKVADL
YPYWGQGTLVTVSSPP (SEQ ID NO:126) or at least about 90% sequence similarity
thereto.~~

42. A compound comprising a structure of:

M-X₁,

X₁-M,

M-L₁-X₁,

X₁-L₁-M,

X₁-M-X₂,

X₂-M-X₁,

X₁-L₁-M-X₂,

X₂-L₁-M-X₁,

X₁-M-L₁-X₂,

X₂-M-L₁-X₁,

X₁-L₁-M-L₂-X₂,

X₂-L₁-M-L₂-X₁,

M-L₁-X₁-L₂-X₂,

M-L₁-X₂-L₂-X₁,

X₁-L₂-X₂-L₁-M, or

X₂-L₂-X₁-L₁-M,

wherein M is an amino acid sequence selected from the group consisting of SEQ ID NOS:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 124, 125 and 126, or at least about 90% sequence similarity thereto,

wherein X₁ is a first biotherapeutic,

wherein X₂ (if present) is a second biotherapeutic,

wherein L₁ (if present) is a first linker having an amino acid sequence selected from the group consisting of (GGGGQ)_n (SEQ ID NO:38), (GGGQ)_n (SEQ ID NO:39), (GGGS)_n (SEQ ID NO:40), (PGPQ)_n (SEQ ID NO:41), (PGPA)_n (SEQ ID NO:42), (GGGG(AP)_nGGGG) (SEQ ID NO:43), (GGE)_n (SEQ ID NO:44), (GGGGGE)_n (SEQ ID NO:45), (GGK)_n (SEQ ID NO:46), (GGGGK)_n (SEQ ID NO:47), (GGGG(EP)_nGGGG) (SEQ ID NO:48), (GGGG(KP)_nGGGG) (SEQ ID NO:49), (PGPE)_n (SEQ ID NO:50), and (PGPK)_n (SEQ ID NO:51), wherein n can be from 1 to 10, and

wherein L₂ (if present) is a second linker having an amino acid sequence selected from the group consisting of SEQ ID NOS:64 and 65, or at least about 90% sequence similarity thereto.

43. The compound of claim 42, wherein the first biotherapeutic is a peptide, protein or oligomer.

44. The compound of claim 42 or 43, wherein the second biotherapeutic is a peptide, protein or oligomer.

45. The compound of any one of claims 42 to 44, wherein the first biotherapeutic and the second biotherapeutic are distinct from one another.

46. The compound of any one of ~~€~~claims 42 to 45, wherein L₁ has an amino acid sequence selected from the group consisting of SEQ ID NOS:52 to 63, or at least about 90% sequence similarity thereto.

47. The compound of any one of ~~€~~claims 42 to 46, wherein the first biotherapeutic and/or the second biotherapeutic is a peptide or protein such as an antibody (Ab) or fragment thereof, adrenocorticotrophic hormone (ACTH), growth/differentiation factor 15 (GDF15), incretin (INC), insulin (INS), interleukin (IL), ciliary neurotrophic factor (CNTF), neuregulin (NRG) or relaxin (RLN).

48. The compound of ~~€~~claim 47, wherein the peptide or protein is an INC.

49. The compound of ~~€~~claim 48, wherein the INC is selected from the group consisting of glucose-dependent insulintropic peptide (GIP), glucagon-like peptide-1 (GLP-1) and GIP/GLP-1.

~~51~~0. The compound of ~~€~~claim 47, wherein the peptide or protein is IL, and wherein the IL is IL-2.

~~51~~1. The compound of ~~€~~claim 47, wherein the peptide or protein is NRG, and wherein the NRG is neuregulin 1 (NRG1) or neuregulin 4 (NRG4).

~~51~~2. The compound of ~~€~~claim 47, wherein the peptide or protein is RLN, and wherein the RLN is relaxin 2 (RLN2).

13. A compound comprising any one of SEQ ID NOS:100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117 or 118, or at least about 90% sequence similarity thereto.

~~53~~14. A pharmaceutical composition comprising a compound of any one of ~~E~~claims 42 to ~~52-13~~ and a pharmaceutically acceptable buffer.

~~54~~15. The pharmaceutical composition of ~~c~~claim ~~53-14~~ further comprising an additional therapeutic agent.

~~55. — A method treating an individual, the method comprising the step of:~~
~~administering to the individual an effective amount of a compound of any one of~~
~~Claims 42 to 52 or a pharmaceutical composition of any one of Claims 53 to 54.~~

~~56. — A compound of any one of Claims 1 to 41 for use in extending the t_{1/2} of a~~
~~biotherapeutic.~~

~~16~~57. A compound of any one of ~~c~~claims 42 to ~~52-13~~ for use in ~~a~~ therapy.

~~58~~17. A compound of any one of ~~E~~claims 42 to ~~52-13~~ for use in treating cardiovascular, neurological, immunological, metabolic, oncological, psychological, pulmonary and/or renal conditions, diseases and/or disorders.

~~59~~18. Use of a compound of any one of ~~E~~claims 42 to ~~52-13~~ for in the manufacture of
manufacturing a medicament for treating cardiovascular, neurological, immunological,
metabolic, oncological, psychological, pulmonary and/or renal conditions, diseases and/or
disorders.

~~60. — A compound comprising any one of SEQ ID NOS:100, 101, 102, 103, 104, 105,~~
~~106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117 or 118, or at least about 90%~~
~~sequence similarity thereto.~~

~~61. — A pharmaceutical composition comprising a compound of Claim 60 and a pharmaceutically acceptable buffer.~~

~~62. — The pharmaceutical composition of Claim 61 further comprising an additional therapeutic agent.~~

~~63. — A method treating an individual, the method comprising the step of:
administering to the individual an effective amount of a compound of Claim 60 or a pharmaceutical composition of any one of Claims 61 to 62.~~

~~64. — A compound of Claim 60 for use in a therapy.~~

~~65. — A compound of Claim 60 for use in treating cardiovascular, neurological, immunological, metabolic, oncological, psychological, pulmonary and/or renal conditions, diseases and/or disorders.~~

~~66. — Use of a compound of Claim 60 for manufacturing a medicament.~~