leakage, through systemic immune activation. These findings illustrate the need for developing therapeutics, such as cytokine therapeutics, that effectively target tumors without the side effects associated with systemic immune activation.

Prodrugs in which a cytokine therapeutic is masked by a masking moiety and in which the therapeutic is only active after cleavage of the masking moiety in the tumor cell environment are one way envisaged for addressing this need.

SUMMARY

This ~~invention~~disclosure provides novel tumor-specific proteolytically cleavable peptide linkers comprising tumor-specific proteolytically cleavable peptides and their use in polypeptide drug constructs for delivering a therapeutic moiety to a tumor cell environment. The part of the construct other than the therapeutic moiety can be considered as a carrier moiety.

The tumor-specific proteolytically cleavable peptide acts as a substrate for protease(s) present in the tumor cell environment. The proteolytically cleavable peptide linker is positioned within the polypeptide drug construct so that the linker cleaves by protease action in the tumor cell environment, and the polypeptide drug construct separates to form cleavage products, one of which will comprise the therapeutic moiety. This ~~invention~~disclosure also relates to cleavage products of said drug constructs, and methods related to the use of the same.

In one aspect, p~~P~~rovided herein is a polypeptide drug construct comprising (i) a therapeutic moiety; (ii) a carrier moiety and (iii) a proteolytically cleavable peptide linker comprising a tumor-specific proteolytically cleavable peptide having an amino acid sequence DLLAVVAAS or ISSGLLSGRS.

In a second aspect, the present disclosure provides a masked cytokine comprising:

a) a first polypeptide chain comprising a masking moiety linked to a first half-life extension moiety via a first linker; and

b) a second polypeptide chain comprising a cytokine moiety thereof linked to a second half-life extension moiety via a second linker,

wherein the first half-life extension moiety is associated with the second half-life extension moiety, and

wherein at least the first linker or the second linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS.

In some ~~embodiment~~examples, the proteolytically cleavable peptide (CP) is flanked on both sides by a spacer domain

(SD1 and SD2) as shown in formula:

SD1-CP-SD2.

In some ~~embodiment~~examples, the spacer domains are rich in amino acid residues G, S and P.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker is from 10 to 25 amino acids in length.

In some ~~embodiment~~examples, the spacer domains only include amino acid residue types selected from the group consisting of G, S and P.

In some ~~embodiment~~examples, the first spacer domain (SD1) is between 3 and 6 amino acids in length.

In some ~~embodiment~~examples, the second spacer domain (SD2) is between 3 and 6 amino acids in length.

In some ~~embodiment~~examples, SD2 comprises the amino acid sequence SGP.

In some ~~embodiment~~examples, SD2 has the amino acid sequence SGP.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker comprises sequence GGPS**DLLAVVAAS**SGP.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker comprises sequence GSGPS**DLLAVVAAS**SGP.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker comprises sequence GSSGGP**DLLAVVAAS**SGP.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker comprises sequence GSP**DLLAVVAAS**SGP.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker comprises sequence GSPG**DLLAVVAAS**SGP.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker comprises sequence GSGSPS**DLLAVVAAS**SGP.

In some ~~embodiment~~examples, the proteolytically cleavable linker comprises sequence GGSSGGSP**ISSGLLSGRS**SGPGSGS.

In some ~~embodiment~~examples, the proteolytically cleavable linker comprises sequence GPPSGSSP**ISSGLLSGRS**SGGG.

In some ~~embodiment~~examples, the proteolytically cleavable linker comprises sequence GGSGGS**ISSGLLSGRS**SGP.

In some ~~embodiment~~examples, the proteolytically cleavable linker comprises sequence GGSGGSGGS**ISSGLLSGRS**SGP.

In some ~~embodiment~~examples, the proteolytically proteolytically cleavable peptide linker is covalently bonded directly to the therapeutic moiety.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker is located within the drug construct between the therapeutic moiety and the carrier moiety.

In some ~~embodiment~~examples, the proteolytically cleavable peptide linker is located within the carrier moiety.

In some ~~embodiment~~examples, the polypeptide drug construct comprises a single polypeptide chain. This means that the therapeutic moiety, the carrier moiety and the proteolytically cleavable peptide linker are present in the same polypeptide chain.

In some ~~embodiment~~examples, the polypeptide drug construct comprises more than one polypeptide chain. In some ~~embodiment~~examples, the proteolytically cleavable peptide linker is present in the same polypeptide chain as the therapeutic moiety. In some ~~embodiment~~examples, the proteolytically cleavable peptide linker is present in a different polypeptide chain to the therapeutic moiety.

In some ~~embodiment~~examples, the polypeptide drug construct is a prodrug. In some ~~embodiment~~examples, where the polypeptide drug construct is a prodrug, the remainder of the molecule (away from which the therapeutic moiety separates after cleavage of the proteolytically cleavable peptide linker) comprises a masking moiety, which inhibits the biological activity of the therapeutic moiety in the prodrug such that the therapeutic moiety is biologically active only after cleavage of the proteolytically cleavable peptide linker in the tumor cell environment In some ~~embodiment~~examples, the masking moiety is present in the same polypeptide chain as the therapeutic moiety. In some ~~embodiment~~examples, the masking moiety is present in a different polypeptide chain to the therapeutic moiety.

In some ~~embodiment~~examples, the masking moiety is present in the same polypeptide chain as the therapeutic moiety.

In some ~~embodiment~~examples, the masking moiety is present in a first polypeptide chain and the therapeutic moiety is present in a second polypeptide chain.

In some ~~embodiment~~examples, the drug construct comprises a half-life extension moiety.

In some ~~embodiment~~examples, the half-life extension moiety comprises an antibody or fragment thereof.

In some ~~embodiment~~examples, the half-life extension moiety comprises first and second half-life extension moieties.

In some ~~embodiment~~examples, the prodrug is a cytokine prodrug where the therapeutic moiety is a cytokine moiety.

In some ~~embodiment~~examples, the masking moiety comprises a domain of the extracellular domain of the cytokine receptor.

A cytokine prodrug as described herein, where the therapeutic moiety is a cytokine moiety and the masking moiety comprises a domain of the extracellular domain of the cytokine receptor is referred to herein as a "masked cytokine".

Provided herein, in some ~~embodiment~~examples, is a masked cytokine comprising a masking moiety in a first polypeptide chain and a cytokine moiety thereof in a second polypeptide chain. Such masked cytokines may be referred to as 'heterodimeric' masked cytokines.

In some ~~embodiment~~examples, the masked cytokine comprises a protein heterodimer comprising:

a) a first polypeptide chain comprising a masking moiety linked to a first half-life extension moiety via a first linker; and

b) a second polypeptide chain comprising a cytokine moiety thereof linked to a second half-life extension moiety via a second linker,

wherein the first half-life extension moiety is associated with the second half-life extension moiety, and wherein at least the first linker or the second linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS.

In some ~~embodiment~~examples, in the first polypeptide chain, the first half life extension domain is linked to the amino terminus of the first linker and the carboxy terminus of the first linker is linked to the amino terminus of the masking moiety and, in the second polypeptide chain, the second half life extension domain is linked to the amino terminus of the second linker and the carboxy terminus of the second linker is linked to the amino terminus of the cytokine moiety thereof.

In some ~~embodiment~~examples, the first polypeptide chain comprises:

N' **HL1-L1-MM** C'

and the second polypeptide chain comprises:

N' **HL2-L2-C** C'

where HL1 is the first half life extension domain, L1 is the first linker, MM is the masking moiety, HL2 is the second half life extension domain, L2 is the second linker, and C is the cytokine moiety,
wherein the first half-life extension moiety is associated with the second half-life extension moiety, and

wherein at least the first linker or the second linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS.

In some ~~embodiment~~examples, the second linker is the proteolytically cleavable linker and the first linker is a non-cleavable linker. This arrangement is described herein as 'Structure A'.

In some ~~embodiment~~examples, the first polypeptide chain comprises:

N' **HL1-non-cleavable L1-MM** C'

and the second polypeptide chain comprises:

N' **HL2-cleavable L2-C** C'

In some ~~embodiment~~examples, the first linker is the proteolytically cleavable linker and the second is a non-cleavable linker. This arrangement is described herein as 'Structure B'.

In some ~~embodiment~~examples, the first polypeptide chain comprises:

N' **HL1- cleavable L1-MM** C'

and the second polypeptide chain comprises:

N' **HL2- non-cleavable L2-C** C'

Provided herein, in some ~~embodiment~~examples, is a masked cytokine comprising a masking moiety and a cytokine moiety thereof linked in a single polypeptide chain. In ~~some embodiments~~another aspect, the present disclosure provides a masked cytokine comprising~~es~~ a polypeptide chain comprising formula:

N' **HL-L2-C-L1-MM** C'

where HL is the half-life extension domain, L1 is the first linker, MM is the masking moiety, L2 is the second linker, and C is the cytokine moiety, wherein at least the first linker comprises a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS. The proteolytically cleavable peptide linker may be as described anywhere herein. In some ~~embodiment~~examples, the first linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS. In some ~~embodiment~~examples, the first linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence ISSGLLSGRS. In some ~~embodiment~~examples, the first linker is a proteolytically cleavable peptide linker and the second linker is non-cleavable. The non-cleavable linker may be as described anywhere herein.

In ~~some embodiments~~another aspect, the present disclosure provides a masked cytokine ~~comprises~~ comprising a polypeptide chain comprising formula:

N' **HL-L2-MM-L1-C** C'

where HL is the half-life extension domain, L1 is the first linker, MM is the masking moiety, L2 is the second linker, and C is the cytokine moiety thereof, wherein at least the first linker comprises a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS. The proteolytically cleavable peptide linker may be as described anywhere herein. In some ~~embodiment~~examples, the first linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS. In some ~~embodiment~~examples, the first linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence ISSGLLSGRS. In some ~~embodiment~~examples, the first linker is a proteolytically cleavable peptide linker and the second linker is non-cleavable. The non-cleavable linker may be as described anywhere herein.

In some ~~embodiment~~examples, the non-cleavable linker is between 3 and 25 amino acids in length.

In some ~~embodiment~~examples, wherein the non-cleavable linker is rich in amino acid residues G, S and P.

In some ~~embodiment~~examples, the non-cleavable linker comprises an amino acid sequence of SEQ ID NO: 14.

In some ~~embodiment~~examples, the non-cleavable linker comprises an amino acid sequence of SEQ ID NO: 23.

In some ~~embodiment~~examples, the half-life extension domain comprises a first half life extension domain and a second half life extension domain.

In some ~~embodiment~~examples, the first half-life extension domain comprises a first Fc domain or a fragment thereof and the second Fc domain comprises an Fc domain or a fragment thereof.

In some ~~embodiment~~examples, the first Fc domain comprises a CH3 domain or a fragment thereof and the second Fc domain comprises a CH3 domain or a fragment thereof.

In some ~~embodiment~~examples, the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof.

In some ~~embodiment~~examples, the first and/ or second Fc domains each contain one or more modifications that promote the non-covalent association of the first and the second half-life extension domains.

In some ~~embodiment~~examples, the first half-life extension domain comprises an IgG1 Fc domain or fragment thereof including the mutations Y349C; T366S; L38A; and Y407V to form a ‘hole’ in the first half-life extension domain and the second half-life extension domain comprises an IgG1 Fc domain or fragment thereof including the mutations S354C and T366W to form the ‘knob’ in the second half-life extension

domain, numbered according to the Kabat EU numbering system.

In some ~~embodiment~~examples, the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof and each comprise an amino substitution at position 297, numbered according to the Kabat EU numbering system.

In some ~~embodiment~~examples, the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof and each comprise the amino substitution N297A, numbered according to the Kabat EU numbering system.

In some ~~embodiment~~examples, the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof and each comprise an amino substitution at position 253, numbered according to the Kabat EU numbering system.

In some ~~embodiment~~examples, the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof and each comprise the amino substitution I253A, numbered according to the Kabat EU numbering system.

In some ~~embodiment~~examples, the first half-life extension domain comprises the amino acid sequence of SEQ ID NO: 9, and the second half-life extension domain thereof comprises the amino acid sequence of SEQ ID NO: 12.

In some ~~embodiment~~examples, the first half-life extension domain comprises the amino acid sequence of SEQ ID NO: 10 and the second half-life extension domain thereof comprises the amino acid sequence of SEQ ID NO: 13.

In some ~~embodiment~~examples, the half life extension domain (HL) comprises an Fc region of an antibody (i.e. the C-terminal region of an immunoglobulin heavy chain) or a fragment thereof comprising dimerized Fc domains (HL1-HL2). Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy-chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. In some ~~embodiment~~examples, the dimerized Fc domains of an antibody (HL1-HL2) comprises a first half life extension domain and a second half life extension domain as described anywhere herein, where the first half-life extension moiety comprises a first Fc domain or a fragment thereof and the second half-life extension moiety comprises a second Fc domain or a fragment thereof. In some ~~embodiment~~examples, HL2 is a component of the polypeptide chain and HL1 is dimerized to HL2.

In some ~~embodiment~~examples, the first and second half-life extension moieties are each an IgG1 Fc domain or fragment thereof. In some ~~embodiment~~examples, the first half-life extension moiety comprises an IgG1 Fc domain or fragment thereof including the mutation I253A and the second half-life extension moiety comprises an IgG1 Fc domain or fragment thereof including the mutation I253A. In some ~~embodiment~~examples, the first and second half-life extension moieties are derived from the sequence for human IgG1 Immunoglobulin heavy constant gamma 1 having SEQ ID NO: 6 (the 'parent sequence'), such that the first and second half-life extension moieties each comprise SEQ ID NO: 7 or fragment thereof, with one or more amino acid modifications. In some ~~embodiment~~examples, the first and second half-life extension moieties comprise SEQ ID NO: 7 with amino substitutions to promote association of the first and second half-life extension moieties according to the 'knob into holes' approach. In some ~~embodiment~~examples, the sequence SEQ ID NO: 7 contains mutations Y349C; T366S; L38A; and Y407V (numbered according to the Kabat EU numbering system) to form the 'hole' in the first half-life extension moiety and mutations S354C and T366W (numbered according to the Kabat EU numbering system) to form the 'knob' in the second half-life extension moiety. In some ~~embodiment~~examples, the first and second half-life extension moieties each further comprise amino substitution N297A, numbered according to the Kabat EU numbering system. In some ~~embodiment~~examples, the first and second half-life extension moieties each further comprise the amino substitution I253A, numbered according to the Kabat EU numbering system. In some ~~embodiment~~examples, the first and second half-life extension moieties each further comprise both the amino substitutions N297A and I253A, numbered according to the Kabat EU numbering system. In some ~~embodiment~~examples, the first half-life extension moiety comprises an amino acid sequence having about or at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of the amino acid sequence of any one of SEQ ID NOs: 7, 8, 9 and 10. In some ~~embodiment~~examples, the second half-life extension moiety comprises an amino acid sequence having about or at least about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of the amino acid sequence of any one of SEQ ID NOs: 7, 11, 12 and 13. In some ~~embodiment~~examples, the cytokine moiety comprises a wild-type cytokine moiety or variant cytokine moiety.

In some ~~embodiment~~examples, the cytokine moiety is an IL-2 cytokine moiety as described anywhere herein.

In some ~~embodiment~~examples, the IL-2 cytokine moiety comprises a wild-type IL-2 cytokine moiety or variant thereof.

In some ~~embodiment~~examples, the IL-2 cytokine moiety comprises an IL-2 cytokine or fragment thereof.

In some ~~embodiment~~examples, the IL-2 cytokine or functional fragment thereof is modified compared to the sequence of a mature IL-2 having SEQ ID NO: 2.

In some ~~embodiment~~examples, the modified IL-2 cytokine or functional fragment thereof comprises modifications R38A, F42A, Y45A, and E62A relative to the sequence of a mature IL-2 having SEQ ID NO: 2.

In some ~~embodiment~~examples, the modified IL-2 cytokine or functional fragment thereof comprises the modification C125A relative to the sequence of a mature IL-2 having SEQ ID NO: 2.

In some ~~embodiment~~examples, the modified IL-2 cytokine or functional fragment thereof comprises R38A, F42A, Y45A, E62A and C125A relative to the sequence of a mature IL-2 having SEQ ID NO: 2.

In some ~~embodiment~~examples, the IL-2 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 3.

In some ~~embodiment~~examples, the masking moiety comprises IL-2Rβ or a fragment, portion or variant thereof.

In some ~~embodiment~~examples, the IL-2Rβ or a fragment, portion or variant thereof comprises an amino acid sequence of SEQ ID NO: 4.

In some ~~embodiment~~examples, the IL-2Rβ or a fragment, portion or variant thereof has a mutation at amino acid positions C122 as compared to IL-2β of SEQ ID NO: 4.

In some ~~embodiment~~examples, the IL-2Rβ or a fragment, portion or variant thereof has a mutation at amino acid positions C168 as compared to IL-2β of SEQ ID NO: 4.

In some ~~embodiment~~examples, the IL-2Rβ or a fragment, portion or variant thereof has mutations at amino acid positions C122 and C168 as compared to IL-2β of SEQ ID NO: 4.

In some ~~embodiment~~examples, the IL-2Rβ or a fragment, portion or variant thereof has mutations C122S and C168S as compared to IL-2β of SEQ ID NO: 4.

In some ~~embodiment~~examples, wherein the IL-2Rβ or a fragment, portion or variant thereof comprises an amino acid sequence of SEQ ID NO: 5.

In some ~~embodiment~~examples, the cytokine moiety is an IL-12 cytokine moiety as described anywhere herein.

In some ~~embodiment~~examples, the IL-12 cytokine moiety comprises a wild-type IL-12 cytokine moiety or variant thereof.

In some ~~embodiment~~examples, the IL-12 cytokine moiety comprises an IL-12 cytokine or fragment thereof.

In some ~~embodiment~~examples, the IL-12 cytokine or functional fragment thereof comprises an IL-12p40 polypeptide or functional fragment thereof covalently linked to an IL-12p35 polypeptide or functional fragment thereof.

In some ~~embodiment~~examples, the IL-12p40 – IL-12p35 linker is between 5 and 20 amino acids in length.

In some ~~embodiment~~examples, the IL-12p40 – IL-12p35 linker is rich in amino acid residues G and S.

In some ~~embodiment~~examples, the IL-12p40 – IL-12p35 linker comprises SEQ ID NO: 116 (GGGGSGGGGSGGGGS).

In some ~~embodiment~~examples, the IL-12p40 polypeptide comprises SEQ ID NO: 204 (as shown in the IL-12 Cytokine Moieties table in the description) or an amino acid sequence having at least one amino acid modification as compared to the amino acid sequence of SEQ ID NO: 204 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p40 polypeptide comprises SEQ ID NO: 204 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p40 polypeptide comprises at least one amino acid modification to the GAG-binding domain (KSKREKKDRV) as compared to the amino acid sequence of SEQ ID NO: 204 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p40 polypeptide comprises SEQ ID NO: 205 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p40 polypeptide comprises SEQ ID NO: 206 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p40 polypeptide comprises an amino acid sequence having one or more cysteine substitution mutations as compared to the amino acid sequence of SEQ ID NO: 204 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p40 polypeptide comprises SEQ ID NO: 207 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p40 polypeptide comprises SEQ ID NO: 208 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p35 polypeptide comprises SEQ ID NO: 209 (as shown in the IL-12 Cytokine Moieties table in the description) or an amino acid sequence having at least one amino acid modification as compared to the amino acid sequence of SEQ ID NO: 209 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12p35 polypeptide comprises SEQ ID NO: 209 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 210 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 211 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 212 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 213 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 214 (as shown in the IL-12 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the masking moiety comprises an IL-12 cytokine receptor, or a subunit or functional fragment thereof.

In some ~~embodiment~~examples, the masking moiety comprises the extracellular domain of human IL-12Rβ1 or a fragment, portion, or variant thereof that retains or otherwise demonstrates an affinity to IL-12.

In some ~~embodiment~~examples, the masking moiety comprises residues 24 to 237 of human IL-12Rβ1, namely a sequence having SEQ ID NO: 215 (as shown in the IL-12 Masking Moieties table in the description).

In some ~~embodiment~~examples, the masking moiety comprises residues 24 to 545 of human IL-12Rβ1, namely a sequence having SEQ ID NO: 216 (as shown in the IL-12 Masking Moieties table in the description).

In some ~~embodiment~~examples, the masking moiety comprises the extracellular domain of human IL-12Rβ2 or a fragment, portion, or variant thereof that retains or otherwise demonstrates an affinity to IL-12.

In some ~~embodiment~~examples, the masking moiety comprises residues 24 to 212 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 217 (as shown in the IL-12 Masking Moieties table in the description).

In some ~~embodiment~~examples, the masking moiety comprises residues 24 to 222 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 218 (as shown in the IL-12 Masking Moieties table in the description), or the masking moiety comprises residues 24 to 227 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 222 (as shown in the IL-12 Masking Moieties table in the description).

In some ~~embodiment~~examples, the masking moiety comprises residues 24 to 319 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 219 (as shown in the IL-12 Masking Moieties table in the description).

In some ~~embodiment~~examples, the masking moiety comprises at least one amino acid modification as compared to the sequence of SEQ ID NO: 219 (as shown in the IL-12 Masking Moieties table in the description), optionally wherein said modifications are cysteine substitution mutations.

In some ~~embodiment~~examples, the masking moiety comprises SEQ ID NO: 220 (as shown in the IL-12 Masking Moieties table in the description).

In some ~~embodiment~~examples, the masking moiety comprises residues 24 to 622 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 221 (as shown in the IL-12 Masking Moieties table in the description).

In some ~~embodiment~~examples, the cytokine moiety is an IL-15 cytokine moiety as described anywhere herein.

In some ~~embodiment~~examples, the IL-15 cytokine moiety comprises a wild-type IL-15 cytokine moiety or variant thereof.

In some ~~embodiment~~examples, the cytokine moiety is an IL-15 cytokine moiety and the masked cytokine further comprises a domain comprising an IL-15Rα subunit or a functional fragment thereof (‘IL-15Rα domain’). In some ~~embodiment~~examples, the cytokine moiety is an IL-15 cytokine moiety and the masked cytokine further comprises a domain comprising an IL-15Rα subunit or a functional fragment thereof (‘IL-15Rα domain’), and the IL-15Rα domain and the IL-15 cytokine moiety are present in different polypeptide chains in the construct and the IL-15Rα domain is non-covalently linked to the IL-15 cytokine moiety.

The ‘IL-15Rα domain’ herein can consist of the sequence of the wild-type sushi domain sIL-15Rα or a variant thereof, such as the sequence of the wild-type sushi domain sIL-15Rα with one or more e.g. 1, 2, 3

or 4 amino acid substitutions. In some ~~embodiment~~examples, the IL-15Rα domain comprises an amino acid substitution at position R26. In some ~~embodiment~~examples, the IL-15Rα domain comprises amino acid substitution R26N. In some ~~embodiment~~examples, the IL-15Rα domain comprises amino acid substitution R26S. In some ~~embodiment~~examples, the IL-15Rα domain comprises an amino acid substitution at position R35. In some ~~embodiment~~examples, the IL-15Rα domain comprises amino acid substitution R35Q. In some ~~embodiment~~examples, the IL-15Rα domain comprises amino acid substitution R35S. In some ~~embodiment~~examples, the IL-15Rα domain comprises an amino acid substitution at positions R26 and R35. In some ~~embodiment~~examples, the IL-15Rα domain comprises amino acid substitutions R26S or R26N, and R35Q or R35S. In some ~~embodiment~~examples, the IL-15Rα domain comprises amino acid substitutions R26N and R35Q.

In some ~~embodiment~~examples, the IL-15 cytokine moiety comprises an IL-15 cytokine or fragment thereof.

In some ~~embodiment~~examples, the IL-15 cytokine or fragment thereof comprises SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description) or a functional fragment thereof.

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having at least one amino acid modification as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having one or more amino acid substitutions at positions D22, E46, E53 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having one or more amino acid substitutions at positions D22, E46, E53, N71, N79, or N112 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having an amino acid substitution at position N71 and N79 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having an amino acid substitution at position N71 and N112 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having an amino acid substitution at position N79 and N112 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having an amino acid substitution at position N71, N79 and N112 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 225 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 226 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 227 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 228 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 229 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 230 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 233 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 234 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 235 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 236 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 237 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 238 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 239 (as shown in the IL-15 Cytokine Moieties table in the description).

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an additional mutation at position N71.

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an additional mutation at position S73.

In some ~~embodiment~~examples, the IL-15 cytokine or functional fragment thereof comprises an additional mutation at one or more of amino acid positions N72, N79, V80, T81, and N112.

In some ~~embodiment~~examples, the masking moiety comprises IL-15Rβ or a fragment or variant thereof.

In some ~~embodiment~~examples, the masking moiety comprises the amino acid sequence of SEQ ID NO: 240 (as shown in the IL-15 Masking Moieties table in the description).

In some ~~embodiment~~examples, the masking moiety comprises IL-15Rβ variant or a fragment thereof having an amino acid substitution at position C122.

In some ~~embodiment~~examples, the masking moiety comprises IL-15Rβ variant or a fragment thereof having amino acid substitution C122S.

In some ~~embodiment~~examples, the masking moiety comprises IL-15Rβ variant or a fragment thereof having an amino acid substitution at position C168.

In some ~~embodiment~~examples, the masking moiety comprises IL-15Rβ variant or a fragment thereof having amino acid substitution C168S.

In some ~~embodiment~~examples, the masking moiety comprises IL-15Rβ variant or a fragment thereof having an amino acid substitution at positions C122 and C168.

In yet another aspect, p~~P~~rovided herein is a cleavage product ~~capable~~ comprising an active therapeutic moiety, preparable by proteolytic cleavage of the proteolytically cleavable linker in the polypeptide drug constructs as described anywhere herein.

Provided herein is a nucleic acid encoding any one of the polypeptide drug constructs as described anywhere herein described herein.

Provided herein is a nucleic acid encoding one of the chains of any one of the polypeptide drug constructs as described anywhere herein described herein.

Provided herein is a vector comprising a nucleic acid described herein.

Provided herein is a vector comprising a nucleic acid encoding a polypeptide drug construct as described anywhere herein described herein.

Provided herein is a vector comprising a nucleic acid encoding one of the chains of a polypeptide drug constructs as described anywhere herein described herein.

In another aspect, the present disclosure provides a host cell comprising a nucleic acid encoding a masked cytokine as described herein. Provided herein is a host cell comprising a nucleic acid described herein.

In one ~~embodiment~~example, the host cell is a HEK cell. In another ~~embodiment~~example, the host cell is a CHO cell.

Provided herein is a composition comprising any one of the polypeptide drug constructs as described anywhere herein described herein.

Provided herein is a pharmaceutical composition comprising any one of the polypeptide drug constructs as described anywhere herein described herein, and a pharmaceutically acceptable carrier.

Provided herein is a kit comprising any one of the polypeptide drug constructs as described anywhere herein, or the compositions, or the pharmaceutical compositions described herein.

Provided herein is a method of producing any one of the polypeptide drug constructs as described anywhere herein, comprising culturing a host cell described herein under a condition that produces the polypeptide drug construct.

Provided herein is a nucleic acid encoding any one of the cleavage products described herein.

Provided herein is a composition comprising any one of the cleavage products described herein.

Provided herein is a pharmaceutical composition comprising any one of the cleavage products described herein, and a pharmaceutically acceptable carrier.

Provided herein is a polypeptide drug construct as described herein for use in medicine.

Provided herein is a cleavage product as described herein for use in medicine.

In another aspect, the present disclosure provides a use of a polypeptide drug construct as described herein in the manufacture of a medicament for treating cancer in a subject. Provided herein is a method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a polypeptide drug construct as described herein.

Provided herein is a method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a composition as described herein.

Provided herein is a method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a pharmaceutical composition as described herein.

Provided herein is a method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a polypeptide drug construct as described herein, whereby the polypeptide drug construct is proteolytically cleaved *in vivo* to produce a cleavage product as described herein.

Provided herein is a method of treating or preventing cancer in a subject, the method comprising a step of producing a cleavage product *in vivo* that is capable of binding to its target protein, where the cleavage product is as described herein.

Provided herein is a polypeptide drug construct as described herein for use in treating or preventing cancer.

Provided herein is a polypeptide drug construct as described herein for use in a method of treating or preventing cancer, the method comprising administering to the subject an effective amount of the polypeptide drug construct, whereby the polypeptide drug construct is proteolytically cleaved *in vivo* to produce a cleavage product as described herein.

Provided herein is a cleavage product as described herein for use in treating or preventing cancer.

Provided herein is a cleavage product as described herein for use in treating or preventing cancer, the method comprising a step of administering a polypeptide drug construct as described herein to a patient,

CLAIMS

1. A polypeptide drug construct comprising (i) a therapeutic moiety; (ii) a carrier moiety and (iii) a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS.

2. A polypeptide drug construct according to claim 1, wherein the proteolytically cleavable peptide (CP) is flanked on both sides by a spacer domain (SD1 and SD2) as shown in formula:

SD1-CP-SD2.

~~3. A polypeptide drug construct according to claim 2, wherein the proteolytically cleavable peptide linker is from 9 to 25 amino acids in length.~~

~~4. A polypeptide drug construct according to claim 2 or claim 3, wherein the spacer domains are rich in amino acid residues G, S and P.~~

~~5. A polypeptide drug construct according to claim 4, wherein the spacer domains only include amino acid residue types selected from the group consisting of G, S and P.~~

~~6.~~3. A polypeptide drug construct according to ~~any one of~~ claim~~s~~ 2 ~~to 5~~, wherein the first spacer domain (SD1) and/or ~~is between 3 and 6 amino acids in length.~~

~~7. A polypeptide drug construct according to any one of claims 2 to 6, wherein the~~ second spacer domain (SD2) is between 3 and 6 amino acids in length.

~~8. A polypeptide drug construct according to any one of claims 2 to 7, wherein the second spacer domain (SD2) comprises the amino acid sequence SGP.~~

~~9. A polypeptide drug construct according to any one of claims 2 to 8, wherein the second spacer domain (SD2) SD2 has the amino acid sequence SGP.~~

~~10. A polypeptide drug construct according to any one of the preceding claims, wherein the proteolytically cleavable peptide linker comprises sequence GGPS**DLLAVVAAS**SGP.~~

~~11. A polypeptide drug construct according to any one of the preceding claims, wherein the proteolytically cleavable peptide linker comprises sequence GSGPS**DLLAVVAAS**SGP.~~

~~12. A polypeptide drug construct according to any one of the preceding claims, wherein the proteolytically cleavable peptide linker comprises sequence GSSGGP**DLLAVVAAS**SGP.~~

~~13. A polypeptide drug construct according to any one of the preceding claims, wherein the proteolytically cleavable peptide linker comprises sequence GSP**DLLAVVAAS**SGP.~~

~~14. A polypeptide drug construct according to any one of the preceding claims, wherein the proteolytically cleavable peptide linker comprises sequence GSPG**DLLAVVAAS**SGP.~~

~~15. A polypeptide drug construct according to any one of the preceding claims, wherein the proteolytically cleavable peptide linker comprises sequence GSGSPS**DLLAVVAAS**SGP.~~

~~16.~~4. A polypeptide drug construct according to ~~any one of the preceding~~ claim~~s~~ 1, wherein the proteolytically cleavable peptide linker is covalently bonded directly to the therapeutic moiety.

~~17. A polypeptide drug construct according to any one of claims 1 to 16, wherein the proteolytically cleavable peptide linker is located within the drug construct between the therapeutic moiety and the carrier moiety.~~

~~18. A polypeptide drug construct according to any one of claims 1 to 15, wherein the proteolytically cleavable peptide linker is located within the carrier moiety.~~

~~19. A polypeptide drug construct according to any one of the preceding claims, wherein the polypeptide drug construct comprises a single polypeptide chain.~~

~~20.~~5. A polypeptide drug construct according to ~~any one of the preceding~~ claim~~s~~ 1, wherein the polypeptide drug construct comprises more than one polypeptide chain.

~~21. A polypeptide drug construct according to claim 20, wherein the proteolytically cleavable peptide linker is present in the same polypeptide chain as the therapeutic moiety.~~

~~22. A polypeptide drug construct according to claim 20, wherein the proteolytically cleavable peptide linker is present in a different polypeptide chain to the therapeutic moiety.~~

~~23. A polypeptide drug construct according to any one of the preceding claims, wherein the polypeptide drug construct is a prodrug.~~

~~24.~~6. A polypeptide drug construct according to ~~any one of the preceding~~ claim~~s~~ 1, further comprising a masking moiety.

~~25. A polypeptide drug construct according to claim 24, wherein the masking moiety is present in the same polypeptide chain as the therapeutic moiety.~~

~~26. A polypeptide drug construct according to claim 24, wherein the masking moiety is present in a different polypeptide chain to the therapeutic moiety.~~

~~27.~~7. A polypeptide drug construct according to ~~any one of the preceding~~ claim~~s~~ 1, wherein the polypeptide drug construct comprises a half-life extension moiety.

~~28. A polypeptide drug construct according to claim 27, wherein the half-life extension moiety comprises an antibody or fragment thereof.~~

~~29. A polypeptide drug construct according to claim 27, wherein the half-life extension moiety comprises first and second half-life extension moieties.~~

~~30. A polypeptide drug construct according to any one of the preceding claims, wherein the prodrug is a cytokine prodrug where the therapeutic moiety is a cytokine moiety.~~

~~31. A cytokine prodrug according to claim 30, wherein the cytokine prodrug comprises a masking moiety and the masking moiety comprises a domain of the extracellular domain of the cytokine receptor.~~

~~32.~~8. A masked cytokine comprising:

a) a first polypeptide chain comprising a masking moiety linked to a first half-life extension moiety via a first linker; and

b) a second polypeptide chain comprising a cytokine moiety thereof linked to a second half-life extension moiety via a second linker,

wherein the first half-life extension moiety is associated with the second half-life extension moiety, and

wherein at least the first linker or the second linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS.

~~33.~~9. A masked cytokine according to claim ~~32~~8, wherein the first polypeptide chain comprises:

N’ **HL1-L1-MM** C’

and the second polypeptide chain comprises:

N' **HL2-L2-C** C'

where HL1 is the first half life extension domain, L1 is the first linker, MM is the masking moiety, HL2 is the second half life extension domain, L2 is the second linker, and C is the cytokine moiety, wherein the first half-life extension moiety is associated with the second half-life extension moiety, and

wherein at least the first linker or the second linker is a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS.

~~34. A masked cytokine according to claim 33, wherein the second linker is the proteolytically cleavable linker and the first linker is a non-cleavable linker.~~

~~35. A masked cytokine according to claim 33, wherein the first linker is the proteolytically cleavable linker and the second linker is a non-cleavable linker.~~

~~36.~~10. A masked cytokine comprising a polypeptide chain comprising formula:

N' **HL-L2-C-L1-MM** C'

where HL is the half-life extension domain, L1 is the first linker, MM is the masking moiety, L2 is the second linker, and C is the cytokine moiety, wherein at least the first linker comprises a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS.

~~37.~~11. A masked cytokine comprising a polypeptide chain comprising formula:

N' **HL-L2-MM-L1-C** C'

where HL is the half-life extension domain, L1 is the first linker, MM is the masking moiety, L2 is the second linker, and C is the cytokine moiety thereof, wherein at least the first linker comprises a proteolytically cleavable peptide linker comprising a proteolytically cleavable peptide (CP) consisting of the amino acid sequence DLLAVVAAS or ISSGLLSGRS.

~~38.~~12. A masked cytokine according to ~~any one of~~ claim~~s 32 to 37~~11, wherein the proteolytically cleavable peptide (CP) is flanked on both sides by a spacer domain (SD1 and SD2) as shown in formula:

SD1-CP-SD2.

~~39. A masked cytokine according to claim 38, wherein the proteolytically cleavable peptide linker is from 9 to 25 amino acids in length.~~

~~40. A masked cytokine according to claim 38 or claim 39, wherein the spacer domains are rich in amino acid residues G, S and P.~~

~~41. A masked cytokine according to claim 40, wherein the spacer domains only include amino acid residue types selected from the group consisting of G, S and P.~~

~~42. A masked cytokine according to any one of claims 38 to 41, wherein the first spacer domain (SD1) is between 3 and 6 amino acids in length.~~

~~43. A masked cytokine according to any one of claims 38 to 42, wherein the second spacer domain (SD2) is between 3 and 6 amino acids in length.~~

~~44. A masked cytokine according to any one of claims 38 to 43, wherein the second spacer domain (SD2) comprises the amino acid sequence SGP.~~

~~45. A masked cytokine according to any one of claims 38 to 44, wherein the second spacer domain (SD2) has the amino acid sequence SGP.~~

~~46. A masked cytokine according to any one of claims 32 to 45, wherein the proteolytically cleavable peptide linker comprises sequence GGPS**DLLAVVAAS**SGP.~~

~~47. A masked cytokine according to any one of claims 32 to 45, wherein the proteolytically cleavable peptide linker comprises sequence GSGPS**DLLAVVAAS**SGP.~~

~~48. A masked cytokine according to any one of claims 32 to 44, wherein the proteolytically cleavable peptide linker comprises sequence GSSGGP**DLLAVVAAS**SGP.~~

~~49. A masked cytokine according to any one of claims 32 to 45, wherein the proteolytically cleavable peptide linker comprises sequence GSP**DLLAVVAAS**SGP.~~

~~50. A masked cytokine according to any one of claims 32 to 45, wherein the proteolytically cleavable peptide linker comprises sequence GSPG**DLLAVVAAS**SGP.~~

~~51. A masked cytokine according to any one of claims 32 to 45, wherein the proteolytically cleavable peptide linker comprises sequence GSGSPS**DLLAVVAAS**SGP.~~

~~52.~~13. A masked cytokine according to claim ~~36 or claim 37~~11, wherein the second linker is a cleavable or non-cleavable linker.

~~53. A masked cytokine according to claim 34, claim 35 or claim 52, wherein the non-cleavable linker is between 3 and 25 amino acids in length.~~

~~54. A masked cytokine according to claim 53, wherein the non-cleavable linker is rich in amino acid residues G, S and P.~~

~~55. A masked cytokine according to claim 53 or claim 54, wherein non-cleavable linker comprises an amino acid sequence of PGSGS (SEQ ID NO: 14).~~

~~56. A masked cytokine according to claim 53 or claim 54, wherein the non-cleavable linker comprises an amino acid sequence of GGSSPPGGGSSGGGSGP (SEQ ID NO: 23).~~

~~57.~~14. A masked cytokine according to claim ~~36 or claim 37~~11, wherein the half-life extension domain comprises a first half life extension domain and a second half life extension domain.

~~58. A polypeptide drug construct according to claim 29, or a masked cytokine according to claim 33 to 35 or claim 57, wherein the first half-life extension domain comprises a first Fc domain or a fragment thereof and the second Fc domain comprises an Fc domain or a fragment thereof.~~

~~59. A polypeptide drug construct or a masked cytokine according to claim 58, wherein the first Fc domain comprises a CH3 domain or a fragment thereof and the second Fc domain comprises a CH3 domain or a fragment thereof.~~

~~60. A polypeptide drug construct or a masked cytokine according to claim 58, wherein the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof.~~

~~61. A polypeptide drug construct or a masked cytokine according to any one of claims 58 to 60, wherein the first and/ or second Fc domains each contain one or more modifications that promote the non-covalent association of the first and the second half-life extension domains.~~

~~62. A polypeptide drug construct or a masked cytokine according to claim 61, wherein the first half-life extension domain comprises an IgG1 Fc domain or fragment thereof including the mutations Y349C; T366S; L38A; and Y407V to form a 'hole' in the first half-life extension domain and the second half-life extension domain comprises an IgG1 Fc domain or fragment thereof including the mutations S354C and T366W to form the 'knob' in the second half-life extension domain, numbered according to the Kabat EU numbering system.~~

~~63. A polypeptide drug construct or a masked cytokine according to claim 61 or claim 62, wherein the~~

~~first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof and each comprise an amino substitution at position 297, numbered according to the Kabat EU numbering system.~~

~~64. A polypeptide drug construct or a masked cytokine according to claim 63, wherein the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof and each comprise the amino substitution N297A, numbered according to the Kabat EU numbering system.~~

~~65. A polypeptide drug construct or a masked cytokine according to any one of claims 61 to 64, wherein the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof and each comprise an amino substitution at position 253, numbered according to the Kabat EU numbering system.~~

~~66. A polypeptide drug construct or a masked cytokine according to claim 65, wherein the first and second half-life extension domains are each an IgG1 Fc domain or fragment thereof and each comprise the amino substitution I253A, numbered according to the Kabat EU numbering system.~~

~~67. A polypeptide drug construct or a masked cytokine according to claim 58, wherein the first half-life extension domain comprises the amino acid sequence of SEQ ID NO: 9, and the second half-life extension domain thereof comprises the amino acid sequence of SEQ ID NO: 12.~~

~~68. A polypeptide drug construct or a masked cytokine according to claim 58, wherein the first half-life extension domain comprises the amino acid sequence of SEQ ID NO: 10 and the second half-life extension domain thereof comprises the amino acid sequence of SEQ ID NO: 13.~~

~~69. A cytokine prodrug according to claim 31 or a masked cytokine according to any one of claims 32 to 68, wherein the cytokine moiety comprises a wild-type cytokine moiety or variant cytokine moiety.~~

~~70.~~15. A ~~cytokine prodrug or a~~ masked cytokine according to claim ~~69~~11, wherein the cytokine moiety is an IL-2 cytokine moiety.

~~71. A cytokine prodrug or a masked cytokine according to claim 70, wherein the IL-2 cytokine moiety comprises an IL-2 cytokine or fragment thereof.~~

~~72. A cytokine prodrug or a masked cytokine according to claim 70 or claim 71, wherein the IL-2~~

~~cytokine or functional fragment thereof is modified compared to the sequence of a mature IL-2 having SEQ ID NO: 2.~~

~~73. A cytokine prodrug or a masked cytokine according to claim 72, wherein the modified IL-2 cytokine or functional fragment thereof comprises modifications R38A, F42A, Y45A, and E62A relative to the sequence of a mature IL-2 having SEQ ID NO: 2.~~

~~74. A cytokine prodrug or a masked cytokine according to claim 72 or claim 73, wherein the modified IL-2 cytokine or functional fragment thereof comprises the modification C125A relative to the sequence of a mature IL-2 having SEQ ID NO: 2.~~

~~75. A cytokine prodrug or a masked cytokine according to claim 72, wherein the modified IL-2 cytokine or functional fragment thereof comprises R38A, F42A, Y45A, E62A and C125A relative to the sequence of a mature IL-2 having SEQ ID NO: 2.~~

~~76. A cytokine prodrug or a masked cytokine according to claim 72, wherein the IL-2 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 3.~~

~~77. A cytokine prodrug or a masked cytokine according to any one of claims 72 to 76, wherein the masking moiety comprises IL-2Rβ or a fragment, portion or variant thereof.~~

~~78. A cytokine prodrug or a masked cytokine according to claim 77, wherein the IL-2Rβ or a fragment, portion or variant thereof comprises an amino acid sequence of SEQ ID NO: 4.~~

~~79. A cytokine prodrug or a masked cytokine according to claim 77, wherein the IL-2Rβ or a fragment, portion or variant thereof has a mutation at amino acid positions C122 as compared to IL-2β of SEQ ID NO: 4.~~

~~80. A cytokine prodrug or a masked cytokine according to claim 77 or claim 79, wherein the IL-2Rβ or a fragment, portion or variant thereof has a mutation at amino acid positions C168 as compared to IL-2β of SEQ ID NO: 4.~~

~~81. A cytokine prodrug or a masked cytokine according to claim 80, wherein the IL-2Rβ or a fragment, portion or variant thereof has mutations at amino acid positions C122 and C168 as compared to IL-2β of SEQ ID NO: 4.~~

~~82. A cytokine prodrug or a masked cytokine according to claim 81, wherein the IL-2Rβ or a fragment, portion or variant thereof has mutations C122S and C168S as compared to IL-2β of SEQ ID NO:~~

~~4.~~

~~83. A cytokine prodrug or a masked cytokine according to claim 77, wherein wherein the IL-2Rβ or a fragment, portion or variant thereof comprises an amino acid sequence of SEQ ID NO: 5.~~

~~84.~~16. A ~~cytokine prodrug or a~~ masked cytokine according to claim ~~69~~11, wherein the cytokine moiety is an IL-12 cytokine moiety.

~~85. A cytokine prodrug or a masked cytokine according to claim 84, wherein the IL-2 cytokine moiety comprises an IL-2 cytokine or fragment thereof.~~

~~86. A cytokine prodrug or a masked cytokine according to claim 85, wherein the IL-12 cytokine or functional fragment thereof comprises an IL-12p40 polypeptide or functional fragment thereof covalently linked to an IL-12p35 polypeptide or functional fragment thereof.~~

~~87. A cytokine prodrug or a masked cytokine according to claim 86, wherein the IL-12p40 – IL-12p35 linker is between 5 and 20 amino acids in length.~~

~~88. A cytokine prodrug or a masked cytokine according to claim 86 or claim 87, wherein the IL-12p40 – IL-12p35 linker is rich in amino acid residues G and S.~~

~~89. A cytokine prodrug or a masked cytokine according to any of claims 86 to 88, wherein the IL-12p40 – IL-12p35 linker comprises SEQ ID NO: 116 (GGGGSGGGGSGGGGS).~~

~~90. A cytokine prodrug or a masked cytokine according to any of claims 86 to 89, wherein the IL-12p40 polypeptide comprises SEQ ID NO: 204 (as shown in the IL-12 Cytokine Moieties table in the description) or an amino acid sequence having at least one amino acid modification as compared to the amino acid sequence of SEQ ID NO: 1(as shown in the IL-12 Cytokine Moieties table in the description).~~

~~91. A cytokine prodrug or a masked cytokine according to claim 90, wherein IL-12p40 polypeptide comprises SEQ ID NO: 1(as shown in the IL-12 Cytokine Moieties table in the description).~~

~~92. A cytokine prodrug or a masked cytokine according to claim 90, wherein IL-12p40 polypeptide comprises at least one amino acid modification to the GAG-binding domain (KSKREKKDRV) as compared to the amino acid sequence of SEQ ID NO: 204 (as shown in the IL-12 Cytokine Moieties table in the description).~~

93. A cytokine prodrug or a masked cytokine according to claim 92, wherein IL-12p40 polypeptide comprises SEQ ID NO: 205 (as shown in the IL-12 Cytokine Moieties table in the description).

94. A cytokine prodrug or a masked cytokine according to claim 92, wherein IL-12p40 polypeptide comprises SEQ ID NO: 206 (as shown in the IL-12 Cytokine Moieties table in the description).

95. A cytokine prodrug or a masked cytokine according to any of claims 90 to 94, wherein IL-12p40 polypeptide comprises an amino acid sequence having one or more cysteine substitution mutations as compared to the amino acid sequence of SEQ ID NO: 204 (as shown in the IL-12 Cytokine Moieties table in the description).

96. A cytokine prodrug or a masked cytokine according to claim 95, wherein the IL-12p40 polypeptide comprises SEQ ID NO: 207 (as shown in the IL-12 Cytokine Moieties table in the description).

97. A cytokine prodrug or a masked cytokine according to claim 95, wherein the IL-12p40 polypeptide comprises SEQ ID NO: 208 (as shown in the IL-12 Cytokine Moieties table in the description).

98. A cytokine prodrug or a masked cytokine according to any of claims 86 to 98, wherein the IL-12p35 polypeptide comprises SEQ ID NO: 209 or an amino acid sequence having at least one amino acid modification as compared to the amino acid sequence of SEQ ID NO: 209 (as shown in the IL-12 Cytokine Moieties table in the description).

99. A cytokine prodrug or a masked cytokine according to claim 98, wherein the IL-12p35 polypeptide comprises SEQ ID NO: 209 (as shown in the IL-12 Cytokine Moieties table in the description).

100. A cytokine prodrug or a masked cytokine according to claim 86, wherein the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 210 (as shown in the IL-12 Cytokine Moieties table in the description).

101. A cytokine prodrug or a masked cytokine according to claim 86, wherein the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 211 (as shown in the IL-12 Cytokine Moieties table in the description).

102. A cytokine prodrug or a masked cytokine according to claim 86, wherein the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 212 (as shown in the IL-12 Cytokine Moieties table in the description).

~~103. A cytokine prodrug or a masked cytokine according to claim 86, wherein the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 213 (as shown in the IL-12 Cytokine Moieties table in the description).~~

~~104. A cytokine prodrug or a masked cytokine according to claim 86, wherein the IL-12 cytokine or functional fragment thereof comprises SEQ ID NO: 214 (as shown in the IL-12 Cytokine Moieties table in the description).~~

~~105. A cytokine prodrug or a masked cytokine according to any of claims 84 to 104, wherein the masking moiety comprises an IL-12 cytokine receptor, or a subunit or functional fragment thereof.~~

~~106. A cytokine prodrug or a masked cytokine according to any of claims 84 to 105, wherein the masking moiety comprises the extracellular domain of human IL-12Rβ1 or a fragment, portion, or variant thereof that retains or otherwise demonstrates an affinity to IL-12.~~

~~107. A cytokine prodrug or a masked cytokine according to claim 106, wherein the masking moiety comprises residues 24 to 237 of human IL-12Rβ1, namely a sequence having SEQ ID NO: 215 (as shown in the IL-12 Masking Moieties table in the description).~~

~~108. A cytokine prodrug or a masked cytokine according to claim 106, wherein the masking moiety comprises residues 24 to 545 of human IL-12Rβ1, namely a sequence having SEQ ID NO: 216 (as shown in the IL-12 Masking Moieties table in the description).~~

~~109. A cytokine prodrug or a masked cytokine according to any of claims 84 to 105, wherein the masking moiety comprises the extracellular domain of human IL-12Rβ2 or a fragment, portion, or variant thereof that retains or otherwise demonstrates an affinity to IL-12.~~

~~110. A cytokine prodrug or a masked cytokine according to claim 109, wherein the masking moiety comprises residues 24 to 212 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 217 (as shown in the IL-12 Masking Moieties table in the description).~~

~~111. A cytokine prodrug or a masked cytokine according to claim 109, wherein the masking moiety comprises residues 24 to 222 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 218 or wherein the masking moiety comprises residues 24 to 227 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 222(as shown in the IL-12 Masking Moieties table in the description).~~

~~112. A cytokine prodrug or a masked cytokine according to claim 109, wherein the masking moiety comprises residues 24 to 319 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 219 (as shown in the IL-12 Masking Moieties table in the description).~~

~~113. A cytokine prodrug or a masked cytokine according to claim 109, wherein the masking moiety comprises at least one amino acid modification as compared to the sequence of SEQ ID NO: 219, optionally wherein said modifications are cysteine substitution mutations (as shown in the IL-12 Masking Moieties table in the description).~~

~~114. A cytokine prodrug or a masked cytokine according to claim 109, wherein the masking moiety comprises SEQ ID NO: 220 (as shown in the IL-12 Masking Moieties table in the description).~~

~~115. A cytokine prodrug or a masked cytokine according to claim 109, wherein the masking moiety comprises residues 24 to 622 of human IL-12Rβ2, namely a sequence having SEQ ID NO: 221 (as shown in the IL-12 Masking Moieties table in the description).~~

~~116.~~17. A ~~cytokine prodrug or a~~ masked cytokine according to claim ~~69~~11, wherein the cytokine moiety is an IL-15 cytokine moiety.

~~117. A cytokine prodrug or a masked cytokine according to claim 116, wherein the IL-2 cytokine moiety comprises an IL-15 cytokine or fragment thereof.~~

~~118. A cytokine prodrug or a masked cytokine according to claim 116 or claim 117, wherein the masked cytokine further comprises a domain comprising an IL-15Rα subunit or a functional fragment thereof ('IL-15Rα domain').~~

~~119. A cytokine prodrug or a masked cytokine according to claim 118, wherein the cytokine moiety is an IL-15 cytokine moiety and the masked cytokine further comprises a domain comprising an IL-15Rα subunit or a functional fragment thereof ('IL-15Rα domain'), and the IL-15Rα domain and the IL-15 cytokine moiety are present in different polypeptide chains in the construct and the IL-15Rα domain is non-covalently linked to the IL-15 cytokine moiety.~~

~~120. A cytokine prodrug or a masked cytokine according to claim 118 or claim 119, wherein the IL-15Rα domain comprises an amino acid substitution at position R26 as compared to the sequence of the wild-type sushi domain sIL-15Rα.~~

~~121. A cytokine prodrug or a masked cytokine according to any one of claims 118 to 120, wherein the IL-15Rα domain comprises an amino acid substitution at position R35 as compared to the sequence of the wild-type sushi domain sIL-15Rα.~~

~~122. A cytokine prodrug or a masked cytokine according to any one of claims 118 to 121, wherein the IL-15Rα domain comprises an amino acid substitution at positions R26 and R35 as compared to the sequence of the wild-type sushi domain sIL-15Rα.~~

~~123. A cytokine prodrug or a masked cytokine according to any one of claims 117 to 120, wherein the IL-15 cytokine or fragment thereof comprises SEQ ID NO: 2 or a functional fragment thereof (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~124. A cytokine prodrug or a masked cytokine according to claim 123, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~125. A cytokine prodrug or a masked cytokine according to any one of claims 117 to 120, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having at least one amino acid modification as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~126. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having one or more amino acid substitutions at positions D22, E46, E53 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~127. A cytokine prodrug or a masked cytokine according to claim 126, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having one or more amino acid substitutions at positions D22, E46, E53, N71, N79, or N112 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~128. A cytokine prodrug or a masked cytokine according to any one of claims 125 to 127, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having an amino acid substitution at position N71 and N79 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~129. A cytokine prodrug or a masked cytokine according any one of claims 125 to 128, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having an amino acid substitution at position N71 and N112 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~130. A cytokine prodrug or a masked cytokine according any one of claims 125 to 129, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having an amino acid substitution at position N79 and N112 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~131. A cytokine prodrug or a masked cytokine according any one of claims 125 to 130, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence having an amino acid substitution at position N71, N79 and N112 as compared to the amino acid sequence of SEQ ID NO: 224 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~132. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 225 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~133. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 226 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~134. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 227 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~135. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 228 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~136. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 229 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~137. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 230 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~138. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 233 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~139. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 234 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~140. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 235 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~141. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 236 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~142. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 237 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~143. A cytokine prodrug or a masked cytokine according to claim 125, wherein the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 238 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~144. A cytokine prodrug or a masked cytokine according to claim 125, wherein, the IL-15 cytokine or functional fragment thereof comprises an amino acid sequence of SEQ ID NO: 239 (as shown in the IL-15 Cytokine Moieties table in the description).~~

~~145. A cytokine prodrug or a masked cytokine according to any one of claims 125 to 131, wherein the IL-15 cytokine or functional fragment thereof comprises an additional mutation at position N71.~~

~~146. A cytokine prodrug or a masked cytokine according to any one of claims 125 to 131 or claim 145, wherein the IL-15 cytokine or functional fragment thereof comprises an additional mutation at position S73.~~

~~147. A cytokine prodrug or a masked cytokine according to any one of claims 125 to 131 or claim 145 or claim 146, wherein the IL-15 cytokine or functional fragment thereof comprises an additional mutation at one or more of amino acid positions N72, N79, V80, T81, and N112.~~

~~148. A cytokine prodrug or a masked cytokine according to any one of claims 116 to 147, wherein, the masking moiety comprises IL-15Rβ or a fragment or variant thereof.~~

~~149. A cytokine prodrug or a masked cytokine according to claim 148, wherein the masking moiety comprises the amino acid sequence of SEQ ID NO: 240 (as shown in the IL-15 Masking Moieties table in the description).~~

~~150. A cytokine prodrug or a masked cytokine according to claim 148, wherein the masking moiety comprises IL-15Rβ variant or a fragment thereof having an amino acid substitution at position C122.~~

~~151. A cytokine prodrug or a masked cytokine according to claim 150, wherein the masking moiety comprises IL-15Rβ variant or a fragment thereof having amino acid substitution C122S.~~

~~152. A cytokine prodrug or a masked cytokine according to claim 148 or claim 150, wherein the masking moiety comprises IL-15Rβ variant or a fragment thereof having an amino acid substitution at position C168.~~

~~153. A cytokine prodrug or a masked cytokine according to claim 152, wherein the masking moiety comprises IL-15Rβ variant or a fragment thereof having amino acid substitution C168S.~~

~~154. A cytokine prodrug or a masked cytokine according to claim 148, wherein the masking moiety comprises IL-15Rβ variant or a fragment thereof having an amino acid substitution at positions C122 and C168.~~

~~155.~~18. A cleavage product ~~capable~~ comprising an active therapeutic moiety, preparable by proteolytic cleavage of the proteolytically cleavable linker in a polypeptide drug construct according to ~~any of~~ claim~~s~~ 1 ~~to 30, a cytokine prodrug according to claim 31, or a masked cytokine according to any of claims 32 to 154~~.

~~156. A nucleic acid encoding a polypeptide drug construct according to any of claims 1 to 30.~~

~~157. A nucleic acid encoding a cytokine prodrug according to claim 31 or a masked cytokine~~

~~according to any of claims 32 to 154.~~

~~158. A nucleic acid encoding a cleavage product according to claim 155.~~

~~159. A nucleic acid encoding one of the polypeptide chains of a polypeptide drug construct according to any of claims 1 to 30.~~

~~160. A nucleic acid encoding one of the polypeptide chains of a cytokine prodrug according to claim 31 or one of the polypeptide chains of a masked cytokine according to any of claims 32 to 154.~~

~~161. A nucleic acid encoding one of the polypeptide chains of a cleavage product according to claim 155.~~

~~162. A vector comprising a nucleic acid according to any one of claims 156 to 161.~~

~~163.~~19. A host cell comprising a nucleic acid encoding a masked cytokine of ~~according to any one of~~ claim~~s 156 to 161~~11.

~~164. A host cell according to claim 163, wherein the host cell is a HEK cell or a CHO cell.~~

~~165. A composition comprising the polypeptide drug construct according to any of claims 1 to 30.~~

~~166. A composition comprising a cytokine prodrug according to claim 31 or a masked cytokine according to any of claims 32 to 154.~~

~~167. A pharmaceutical composition comprising the polypeptide drug construct according to any of claims 1 to 30 and a pharmaceutically acceptable carrier.~~

~~168. A pharmaceutical composition comprising a cytokine prodrug according to claim 31 or a masked cytokine according to any of claims 32 to 154 and a pharmaceutically acceptable carrier.~~

~~169. The pharmaceutical composition of claim 167 or claim 168, wherein the pharmaceutical composition is in single unit dosage form.~~

~~170. The pharmaceutical composition of claim 169, wherein the pharmaceutical composition is formulated for intravenous administration and is in single unit dosage form.~~

~~171. The pharmaceutical composition of claim 169, wherein the pharmaceutical composition is formulated for injection and is in single unit dosage form.~~

~~172. The pharmaceutical composition of claim 169, wherein the pharmaceutical composition is a liquid and is in single unit dosage form.~~

~~173. A kit comprising a polypeptide drug construct according to any of claims 1 to 30, or a cytokine prodrug according to claim 31, or a masked cytokine according to any of claims 32 to 154, or the composition of claim 165 or claim 166, or the pharmaceutical composition of claims 167 to 172.~~

~~174. A method of producing a masked cytokine as defined in any one of claims 32 to 154 comprising culturing the host cell of claim 82 under a condition that produces the masked IL-12 cytokine.~~

~~175. A composition comprising the cleavage product of claim 155.~~

~~176. A pharmaceutical composition comprising the cleavage product of claim 155, and a pharmaceutically acceptable carrier.~~

~~177. A polypeptide drug construct according to any of claims 1 to 30 for use in medicine.~~

~~178. A cytokine prodrug according to claim 31 for use in medicine.~~

~~179. A masked cytokine according to any of claims 32 to 154 for use in medicine.~~

~~180. A composition according to claim 165 or claim 166 for use in medicine.~~

~~181. A pharmaceutical composition according to claims 167 to 172 for use in medicine.~~

~~182. A cleavage product according to claim 155 for use in medicine.~~

~~183.~~20. ~~A method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount~~ Use of a polypeptide drug construct according to ~~any of~~ claim~~s~~ 1 ~~to 30~~ in the manufacture of a medicament for treating cancer in a subject.

~~184. A method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a cytokine prodrug according to claim 31.~~

~~185. A method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a masked cytokine according to any of claims 32 to 154.~~

~~186. A method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a composition according to claim 165 or claim 166.~~

~~187. A method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a pharmaceutical composition according to claims 167 to 172.~~

~~188. A method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of a cleavage product according to claim 155.~~

~~189. A method of treating or preventing cancer in a subject, the method comprising administering to the subject an effective amount of or a cytokine prodrug according to claim 31, or a masked cytokine according to any of claims 32 to 154, whereby the cytokine prodrug or masked cytokine is proteolytically cleaved *in vivo* to produce a cleavage product as defined in claim 155.~~

~~190. A method of treating or preventing cancer in a subject, the method comprising a step of producing a cleavage product *in vivo* that is capable of binding to its cognate receptor, where the cleavage product is as defined claim 155.~~

~~191. A method according to any one of claims 183 to 190, wherein the cancer is a solid tumor.~~

~~192. A masked IL-12 cytokine as defined in any one of claims 1 to 72 for use in treating or preventing cancer.~~

~~193. A masked IL-12 cytokine as defined in any one of claims 1 to 72 for use in a method of treating or preventing cancer, the method comprising administering to the subject an effective amount of the masked IL-12 cytokine, whereby the masked cytokine is proteolytically cleaved *in vivo* to produce a cleavage product as defined in any one of claims 73 to 79.~~

~~194. A masked IL-12 cytokine for use according to claim 103, wherein the cancer is a solid tumor.~~

~~195. A polypeptide drug construct according to any of claims 1 to 30 for use in treating or preventing cancer.~~

~~196. A cytokine prodrug according to claim 31 for use in treating or preventing cancer.~~

~~197. A masked cytokine according to any of claims 32 to 154 for use in treating or preventing cancer.~~

~~198. A composition according to claim 165 or claim 166 for use in treating or preventing cancer.~~

~~199. A pharmaceutical composition according to claims 167 to 172 for use in treating or preventing cancer.~~

~~200. A cleavage product according to claim 155 for use in treating or preventing cancer.~~

~~201. A polypeptide drug construct according to claim 195, a cytokine prodrug for use according to claim 196, a masked cytokine for use according to claim 197, a composition for use according to claim 198, a pharmaceutical composition for use according to claim 199, or a cleavage product for us according to claim 200 wherein the cancer is a solid tumor.~~

~~202. A cleavage product as defined in claim 155 for use in a method of treating or preventing cancer, the method comprising a step of administering a polypeptide drug construct according to any of claims 1 to 30, a cytokine prodrug according to claim 31, or a masked cytokine according to any of claims 32 to 154. to a patient, thereby producing the cleavage product by proteolytic cleavage of the proteolytically cleavable peptide linker *in vivo*.~~

~~203. A cleavage product as defined in claim 155 for use in a method of treating or preventing cancer in a subject, the method comprising a step of producing the cleavage product by *in vivo* proteolytic cleavage of a polypeptide drug construct according to any of claims 1 to 30, a cytokine prodrug according to claim 31, or a masked cytokine according to any of claims 32 to 154 that has been administered to the subject.~~