impacted by IL-6 dysregulation.

SUMMARY ~~OF THE INVENTION~~

The present disclosure is directed to individual peptide immunogen constructs targeting Interleukin 6 (IL-6) and formulations thereof for immunotherapy of diseases impacted by IL-6 dysregulation.

These individual IL-6 peptide immunogen constructs have 30 or more amino acids in length comprising functional B cell epitopes derived from the IL-6 Receptor binding regions E42-C83 (SEQ ID NO: 16) or N144-I166 (SEQ ID NO: 19) or fragments thereof, which are linked through spacer residue(s) to heterologous T helper cell (Th) epitopes derived from pathogen proteins. These IL-6 peptide constructs, containing both designed B cell- and Th cell epitopes act together to stimulate the generation of highly specific antibodies directed against IL-6R binding region, offering therapeutic immune responses to subjects predisposed to, or suffering from, a disease impacted by IL-6 dysregulation.

In some ~~embodiments~~examples, the disclosed IL-6 peptide immunogen constructs comprise a hybrid peptide having a B cell antigenic site (SEQ ID NOs: 5-20; 72-74, shown in **Table 1**) derived from the IL-6R binding region or fragments thereof, that is linked to a heterologous Th epitope derived from pathogenic proteins (SEQ ID NOs: 78-106 and 216-226, shown in **Table 2**) that act together to stimulate the generation of highly specific antibodies that are cross-reactive with the recombinant human IL-6 (SEQ ID NO: 1), or IL-6 of other species such as macaque (SEQ ID NO: 2), mouse (SEQ ID NO: 3), and rat IL-6 (SEQ ID NO: 4).

In some aspects, the present disclosure is directed to a use of a IL-6 peptide immunogen construct in the manufacture of a medicament for preventing and/or treating a disease impacted by IL-6 dysregulation in an animal, wherein the disease impacted by IL-6 dysregulation is rheumatoid arthritis, wherein the IL-6 peptide immunogen construct is selected from the group consisting of SEQ ID NOs: 107, 116, 118, 124-129, 131-145, 148, and 157.

In another aspect, the present disclosure is directed to a composition comprising a IL-6 peptide immunogen construct selected from the group consisting of SEQ ID NOs: 107, 116, 118, 124-129, 131-145, 148, and 157.

In another aspect, the present disclosure is directed to a pharmaceutical composition comprising: a IL-6 peptide immunogen construct selected from the group consisting of SEQ ID NOs: 107, 116, 118, 124-129, 131-145, 148, and 157; and a pharmaceutically acceptable delivery vehicle and/or adjuvant.

In another aspect, the present disclosure is directed to a use of the pharmaceutical composition according to the disclosure in the manufacture of a medicament for preventing and/or treating a disease impacted by IL-6 dysregulation in an animal, wherein the disease impacted by IL-6 dysregulation is rheumatoid arthritis.

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CLAIMS

~~1. An IL-6 peptide immunogen construct having about 30 or more amino acids, represented by the formulae:~~

~~$(Th)_m$-$(A)_n$-(IL-6R binding region of IL-6 or a fragment thereof)-X~~

~~or~~

~~(IL-6R binding region of IL-6 or a fragment thereof)-$(A)_n$-$(Th)_m$-X~~

~~or~~

~~$(Th)_m$-$(A)_n$-(IL-6R binding region of IL-6 or a fragment thereof)-$(A)_n$-$(Th)_m$-X~~

~~wherein~~

~~Th is a heterologous T helper epitope;~~

~~A is a heterologous spacer;~~

~~(IL-6R binding region of IL-6 or a fragment thereof) is selected from the group consisting of SEQ ID NOs: 5-19;~~

~~X is an α-COOH or α-$CONH_2$ of an amino acid;~~

~~m is from 1 to about 4; and~~

~~n is from 0 to about 10.~~

~~2. The IL-6 peptide immunogen construct according to claim 1, wherein the Th epitope is selected from the group consisting of SEQ ID NOs: 78-106 and 216-226.~~

~~3~~1. ~~The~~ Use of a IL-6 peptide immunogen construct in the manufacture of a medicament for preventing and/or treating a disease impacted by IL-6 dysregulation in an animal, wherein the disease impacted by IL-6 dysregulation is rheumatoid arthritis, ~~according to claim 1,~~ wherein the IL-6 peptide immunogen construct is selected from the group consisting of SEQ ID NOs: 107, 116, 118, 124-129, 131-145, 148, and 157~~107-215~~.

~~4. An IL-6 peptide immunogen construct comprising:~~

~~a. a B-cell epitope selected from the group consisting of SEQ ID NOs: 5 to 19;~~

~~b. a T helper epitope comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 78-106, 216-226, and any combination thereof; and~~

~~c. an optional heterologous spacer selected from the group consisting of an amino acid, Lys , Gly , Lys Lys Lys , (α, ε N)Lys, ε N Lys Lys Lys Lys (SEQ ID NO: 77), Lys Lys Lys ε N-Lys (SEQ ID NO: 231), and Pro-Pro-Xaa-Pro-Xaa-Pro (SEQ ID NO: 76), and any combination thereof,~~

~~wherein the B-cell epitope is covalently linked to the T helper epitope directly or through the optional heterologous spacer.~~

~~5. The IL-6 peptide immunogen construct of claim 4, wherein the T helper epitope is selected from the group consisting of SEQ ID NOs: 78 to 106, and any combination thereof.~~

~~6. The IL-6 peptide immunogen construct of claim 4, wherein the optional heterologous spacer is (α, ε N)Lys, ε N Lys Lys Lys Lys (SEQ ID NO: 77), Lys Lys Lys ε N Lys (SEQ ID NO: 231), or Pro Pro Xaa Pro Xaa Pro (SEQ ID NO: 76), and any combination thereof.~~

~~7. The IL-6 peptide immunogen construct of claim 4, wherein the T helper epitope is covalently linked to the amino terminus of the B-cell epitope.~~

~~8. The IL-6 peptide immunogen construct of claim 4, wherein the T helper epitope is covalently linked to the amino terminus of the B-cell epitope through the optional heterologous spacer.~~

~~9~~2. A composition comprising ~~the~~ a IL-6 peptide immunogen construct selected from the group consisting of SEQ ID NOs: 107, 116, 118, 124-129, 131-145, 148, and 157~~according to claim 1~~.

~~10~~3. A pharmaceutical composition comprising:

a. ~~the~~ a IL-6 peptide immunogen construct selected from the group consisting of SEQ ID NOs: 107, 116, 118, 124-129, 131-145, 148, and 157~~according to claim 1~~; and

b. a pharmaceutically acceptable delivery vehicle and/or adjuvant.

~~11. The pharmaceutical composition of claim 10, wherein~~

~~a. the IL-6R binding region or fragment thereof is selected from the group consisting of SEQ ID NOs: 5-19;~~

~~b. the Th epitope is selected from the group consisting of SEQ ID NOs: 78-106 and 216-226; and~~

~~c. the heterologous spacer is selected from the group consisting of an amino acid, Lys , Gly , Lys Lys Lys , (α, ε N)Lys, ε N Lys Lys Lys Lys (SEQ ID NO: 77), Lys Lys Lys ε N Lys (SEQ ID NO: 231), and Pro Pro Xaa Pro Xaa Pro (SEQ ID NO: 76), and any combination thereof; and~~

~~wherein the IL-6 peptide immunogen construct is mixed with an CpG oligodeoxynucleotide (ODN) to form a stabilized immunostimulatory complex.~~

~~12~~4. The pharmaceutical composition of claim ~~10~~3, wherein

~~a. the IL-6 peptide immunogen construct is selected from the group consisting of SEQ ID NOs: 107-215; and~~

~~wherein~~ the IL-6 peptide immunogen construct is mixed with an CpG oligodeoxynucleotide (ODN) to form a stabilized immunostimulatory complex.

~~13. Use of the pharmaceutical composition according to claim 10 in the generation of antibodies against IL-6 in an animal.~~

~~14. An isolated antibody or epitope binding fragment thereof that specifically binds to the IL-6R binding region of IL-6 or a fragment thereof in the IL-6 peptide immunogen construct according to claim 1.~~

~~15. The isolated antibody or epitope binding fragment thereof according to claim 14 bound to the IL-6 peptide immunogen construct.~~

~~16. A composition comprising the isolated antibody or epitope binding fragment thereof according to claim 14.~~

~~17~~5. Use of the pharmaceutical composition according to claim ~~10~~ 3 in the manufacture of a medicament for preventing and/or treating a disease impacted by IL-6 dysregulation in an animal, wherein the disease impacted by IL-6 dysregulation is rheumatoid arthritis.