



(51) International Patent Classification:

A61K 47/48 (2006.01) A61P 35/02 (2006.01)
A61P 35/00 (2006.01) A61P 37/00 (2006.01)

(21) International Application Number:

PCT/US2016/015983

(22) International Filing Date:

1 February 2016 (01.02.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/111,069 2 February 2015 (02.02.2015) US

(71) Applicant: THE UNIVERSITY OF BIRMINGHAM
[GB/GB]; Edgbaston, Birmingham B15 2TT (GB).

(72) Inventors; and

(71) Applicants (for US only): COBBOLD, Mark [GB/US]; 5
Everett Avenue, Winchester, Massachusetts 01890 (US).
MILLAR, David [GB/US]; 83 Church Street, Apartment
128, Winchester, Massachusetts 01890 (US).

(74) Agent: MCNEILL, Rebecca; McNeill Baur PLLC, 125
Cambridge Park Drive, Suite 301, Cambridge, Massachu-
setts 02140 (US).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

— with amended claims (Art. 19(1))

Date of publication of the amended claims: 15 September 2016

(54) Title: TARGETING MOIETY PEPTIDE EPITOPE COMPLEXES HAVING A PLURALITY OF T-CELL EPITOPES

(57) Abstract: A variety of targeting moiety peptide epitope complexes (TPECs) are described in different embodiments. In each of the embodiments, however, a targeting moiety may be used to deliver the TPEC to an area of unwanted cells, allowing for a therapeutic effect to be delivered locally. The TPEC also contains a plurality of T-cell epitopes. The TPEC further comprises cleavage sites that release the T-cell epitopes from the targeting agent, and in some embodiments from each other, when they are in the microenvironment of the unwanted cells. Although the arrangement and number of T-cell epitopes varies in different embodiments described herein, once cleaved from the targeting agent (and any neighboring T-cell epitopes), the T-cell epitopes function by stimulating an immune response against the unwanted cells.



AMENDED CLAIMS
received by the International Bureau on 02 August 2016 (02.08.2016)

What is Claimed is:

1. A composition for retargeting an immune response to unwanted cells comprising a TPEC wherein:
 - a. T is a targeting moiety that is capable of targeting unwanted cells;
 - b. L is at least one linker capable of linkage to T where L is a peptide bond, at least one peptide, or a chemical linker;
 - c. C is at least one cleavage site
 - i. cleaved by an enzyme expressed by the unwanted cells;
 - ii. cleaved through a pH-sensitive cleavage reaction inside the unwanted cell;
 - iii. cleaved by a complement-dependent cleavage reaction; or
 - iv. cleaved by a protease that is colocalized to the unwanted cell by a targeting moiety that is the same or different from the targeting moiety in the TPEC; and
 - d. E is at least one T-cell epitope,wherein the L, C, and E moieties are arranged in at least one of the following patterns:
 - i. a plurality of L-C-E, each attached separately to T,
 - ii. at least one of L-(C-E)_n, wherein n is an integer of at least 2 (optionally from about 2 to 50) and with each C-E attached to the L in parallel, and/or
 - iii. at least one of L-(C-E)_n, wherein n is an integer of at least 2 (optionally from about 2 to 50) and with each C-E attached to the L in series.
2. A composition for retargeting an immune response to unwanted cells comprising a TPEC having:
 - a. a targeting moiety that is capable of targeting unwanted cells;
 - b. a plurality of more than 10 T-cell epitopes conjugated to the targeting moiety with at least one cleavage site, wherein the cleavage site is
 - i. cleaved by an enzyme expressed by the unwanted cells;
 - ii. cleaved through a pH-sensitive cleavage reaction inside the unwanted cell;

- iii. cleaved by a complement-dependent cleavage reaction; or
 - iv. cleaved by a protease that is colocalized to the unwanted cell by a targeting moiety that is the same or different from the targeting moiety in the TPEC.
3. The composition of claim 1, wherein the plurality of T-cell epitopes are individually conjugated to the targeting moiety, each T-cell epitope by a cleavage site.
 4. The composition of claim 1, wherein the plurality of T-cell epitopes are conjugated as at least one bundle to the targeting moiety by one cleavage site.
 5. The composition of claim 1, wherein the T-cell epitopes within a bundle have cleavage sites between them.
 6. The composition of claims 1, wherein the plurality of T-cell epitopes are not all identical.
 7. The composition of claim 1, wherein the at least one cleavage site and the plurality of T-cell epitopes are conjugated to the targeting agent through a Sulfo-SMCC, SMCC, or maleimide linkage.
 8. The composition of claim 1, wherein at least one T-cell epitope is an MHC Class I restricted peptide.
 9. The composition of claim 1, wherein at least one T-cell epitope is an MHC Class II restricted peptide.
 10. The composition of claim 1, wherein the plurality of T-cell epitopes are from about 7 to about 14 amino acids in length.
 11. The composition of claim 1, wherein the agent comprises at least about 2, 3, 4, 5, 6, 7, 8, 9, or 10 T cell epitopes.
 12. The composition of claim 1, wherein the T-cell epitopes are chosen from CMV, influenza, EBV, hepatitis, chicken pox, mumps, measles, diphtheria, Haemophilus influenzae, rubella, pertussis, polio, pneumococcus, rotavirus, tetanus, vaccinia, and yellow fever T-cell epitopes.
 13. The composition of claim 1, wherein the composition comprises T-cell epitopes from at least two different infectious agents.

14. The composition of claim 1, wherein the T-cell epitopes are chosen from HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, HLA-G, CD1d, and MR1.
15. The composition of claim 1, wherein the T-cell epitopes are chosen from HLA-A*01, HLA-A*02, HLA-A*03, HLA-A*11, HLA-B*44, HLA-B*07, HLA-B*08, HLA-B*15, HLA-B*35, HLA-B*40, HLA-C*07, HLA-C*03, HLA-C*05, HLA-C*04, HLA-C*06, and HLA-E*0101 restricted antigens.
16. The composition of claim 1, wherein the composition comprises at least the following T-cell epitopes: HLA-A*02, HLA-A*01, and HLA-A*03.
17. The composition of claim 1, wherein the T-cell epitopes comprise at least one of SEQ ID NOS: 1-2, 5-7, 15-57.
18. The composition of claim 1, wherein the targeting moiety is an antibody or functional part thereof.
19. The composition of claim 1, wherein the T-cell epitopes are flanked on one or both ends by at least one human protein domain.
20. The composition of claim 1, wherein the cleavage site is capable of being cleaved outside the unwanted cells.
21. The composition of claim 1, wherein the enzyme expressed by the unwanted cells is a protease.
22. The composition of claim 1, wherein the unwanted cells are cancer cells.
23. A method of treating a disease in a patient characterized by the presence of unwanted cells comprising administering a composition of claim 1 to the patient.
24. A method of retargeting an immune response of a patient to unwanted cells comprising administering a composition of claim 1 to the patient.
25. The composition of claim 18, wherein the antibody or functional part thereof is an anti-CEA or anti-CEACAM antibody or functional part thereof.
26. The composition of claim 2, wherein the targeting moiety is an antibody or functional part thereof.
27. The composition of claim 26, wherein the antibody or functional part thereof is an anti-CEA or anti-CEACAM antibody or functional part thereof.

28. The method of claim 23, wherein the targeting moiety is an antibody or functional part thereof and the antibody or functional part thereof is optionally an anti-CEA or anti-CEACAM antibody or functional part thereof.

29. The method of claim 24, wherein the targeting moiety is an antibody or functional part thereof and wherein the antibody or functional part thereof is optionally an anti-CEA or anti-CEACAM antibody or functional part thereof.