Abstract:

Title: COMPOSITIONS AND METHODS OF CHIMERIC AUTOANTIBODY RECEPTOR T CELLS

The invention includes compositions comprising at least one chimeric autoantibody receptor (CAAR) specific for an autoantibody, vectors comprising the same, compositions comprising CAAR vectors packaged in viral particles, and recombinant T cells expressing the CAAR. The invention also includes methods of making a genetically modified T cell expressing a CAAR (CAART) wherein the expressed CAAR comprises a desmoglein extracellular domain.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/28872

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) ... Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300
Form PCT/ISA/210 (second sheet) (January 2015)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) ... C07K 14/705, C07K 19/00, C07K 14/47 (2015.01)
CPC - C07K 2318/20, C07K 14/705, C07K 19/00, C07K 14/4713

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 35/17, C07K 14/70517, A61K 2039/5158, C07K 16/28
(keyword limited; terms below)

Electronic database consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, Google Patents; Search terms: chimeric autoantibody receptor, CAAR, autoimmune, autoantibody, autoAb, T cell, T lymphocyte, CD6, CD137, 4-1BB, CD3, treat, therapy, pemphigus vulgaris, paraneoplastic pemphigus foliaceus, Dsg1, Dsg-1, Dsg, desmoglein 1, desmoglein-1, intracellular,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
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<tbody>
<tr>
<td>Y</td>
<td>US 2014/050708 A1 (POWELL et al.) 20 February 2014 (20.02.2014) para [0008], [0022], [0023], [0066], [0068], [0084], [0132], [0133], [0134], [0135], [0136], [0151], [0160], [0160], [0199], [0271], [0332]</td>
<td>1-2, 6-13, (16-18)(1,2,6-13), 19-20, 22-23, 26-31, (34-39)/(20,22,23,26-31)</td>
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<td>Y</td>
<td>US 2005/01 18676 A1 (QI et al.) 02 June 2005 (02.06.2005) para [0011], [0066], [0068]; SEQ ID NOs: 1 and 3</td>
<td>11, (16-18)/1 1, 29, (34-39)/29</td>
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<td>Y</td>
<td>US 2001/0024831 A1 (DER MAUR et al.) 27 September 2001 (27.09.2001) para [0023], [0111]; SEQ ID NO: 4</td>
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Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed
  "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  "Z" document member of the same patent family

Date of the actual completion of the international search
29 September 2015 (29.09.2015)

Date of mailing of the international search report
23 OCT 2015

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer:
Lee W. Young
PCT Helpdesk: 571-272-4300
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Form PCT/ISA/210 (second sheet) (January 2015)
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</table>
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/28872

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

— please see continuation on next extra sheet —

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.: 1-2, 6-13, 16-18 (in part), 19-20, 22-23, 26-31, 34-39 (in part), where the autoantigen is Dsg1 and the intracellular signaling domain is CD137 intracellular domain of SEQ ID NO: 15

Remark on Protest  ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)
Continuation of: Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group Ia: Claims 1-39, drawn to an isolated nucleic acid sequence encoding a chimeric autoantibody receptor (CAAR) or an isolated CAAR polypeptide. The CAAR comprising an autoantigen and an intracellular signaling domain will be searched to the extent that:
- the autoantigen is Dsg1 (claims 2 and 20), and
- the intracellular signaling domain is CD137 intracellular domain of SEQ ID NO: 15 (claims 12-13 and 30-31).

It is believed that claims 1-2, 6-13, 16-18 (in part), 19-20, 22-23, 26-31, 34-39 (in part), encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass a CAAR comprising an autoantigen Dsg1 and an CD137 intracellular domain of SEQ ID NO: 15. Additional CAAR(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected CAAR. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "*" group(s) will result in only the first claimed invention to be searched. An exemplary election would be a CAAR comprising: the autoantigen is Dsg3 of SEQ ID NO: 3 including a Dsg3 peptide of SEQ ID NO:2, and the intracellular signaling domain is CD137 intracellular domain of SEQ ID NO: 15, i.e. claims 1-13, 16-18 (in part), 19-31, 34-39 (in part).

Group Ii: Claims 40-43, drawn to a method for treating an autoimmune disease in a subject by administering to the subject an effective amount of a genetically modified T cell comprising an isolated nucleic acid sequence encoding a chimeric autoantibody receptor (CAAR).

The inventions listed as Groups Ia and Ii do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

The technical feature of each of the inventions listed as Group Ia is the specific isolated CAAR nucleic acid or polypeptide recited therein. Each invention requires a unique autoantigen and intracellular signaling domain not required by any of the other inventions.

Group Ii requires treating an autoimmune disease in a subject by administering to a subject an effective amount of a genetically modified T cell, not required by Group Ia.

Common Technical Features

The feature shared by Groups Ia and Ii is (claim 1) an isolated nucleic acid sequence encoding a chimeric autoantibody receptor (CAAR), wherein the isolated nucleic acid sequence comprises an extracellular domain comprising an autoantigen or fragment thereof, a nucleic acid sequence of a transmembrane domain, and a nucleic acid sequence of an intracellular signaling domain.

Another feature shared by the inventions of Group Ia is (claim 16) a vector comprising an isolated nucleic acid sequence encoding CAAR.

Another feature shared by the inventions of Group Ia is (claim 19) an isolated chimeric autoantibody receptor (CAAR) comprising an extracellular domain comprising an autoantigen or fragment thereof, a transmembrane domain, and an intracellular signaling domain.

Another feature shared by the inventions of Group Ia is (claim 34) a genetically modified cell comprising a CAAR.

— please see continuation on next extra sheet —
However, these shared technical features do not represent a contribution over prior art, because the shared technical features are taught by US 2011/0050708 A1 to Powell et al. (hereinafter "Powell") in view of the article entitled "The anti-desmoglein 1 autoantibodies in pemphigus vulgaris sera are pathogenic" by Ding et al. (J Invest Dermatol, May 1999, Vol 112, No 5, pages 739-43) (hereinafter "Ding"). and further in view of US 2006/0257420 A1 to Zimmerman.

Powell discloses [claims 1 and 19] an isolated nucleic acid sequence encoding a chimeric receptor (para [0008]) "The present invention provides an isolated nucleic acid sequence encoding a chimeric antigen receptor (CAR)"); and an isolated chimeric receptor (para [0021]). The invention also provides an isolated CAR®, wherein the chimeric receptor comprises an extracellular domain (para [0133]) "The CAR of the invention can be engineered to comprise an extracellular domain having an antigen binding domain fused to an intracellular signaling domain"; para [0135] The present invention provides chimeric antigen receptor (CAR) comprising an extracellular and an intracellular domain").

a transmembrane domain (para [0136] "Between the extracellular domain and the transmembrane domain of the CAR"; para [0151]) "Preferably, the transmembrane domain in the CAR of the invention is the CD8 transmembrane domain"); and an intracellular signaling domain of a costimulatory molecule (para [0135] "Intracellular domain from one or more of a costimulatory molecule and a zeta chain. Preferably, the antigen binding moiety is fused with one or more intracellular domains selected from the group of a CD137 (4-1BB) signaling domain, a CD28 signaling domain, a CD3ζa signal domain, and any combination thereof; para [0134] "In one embodiment, the CAR of the invention comprises a CD137 (4-1BB) signaling domain").

Powell does not teach that the chimeric receptor is a chimeric autoantibody receptor, wherein the extracellular domain comprises an autoantigen or fragment thereof. However, Powell does teach that the extracellular domain can comprise a target-specific binding element (para [0135] "extracellular domain comprises a target-specific binding element") where the target-specific binding element can be targeted to a ligand of an autoimmune disease (para [0138] "In one embodiment, the CAR of the invention comprises a target-specific binding element other referred to as an antigen binding moiety... examples of cell surface markers that may act as ligands for the antigen moiety domain in the CAR of the invention include those associated with autoimmune disease"). Powell further teaches that the autoimmune disease treated using the chimeric receptor is the result of inappropriate and excessive response to a autoantigen, where the disease can be pemphigus vulgaris (para [0084] "An autoimmune disease is the result of an inappropriate and excessive response to a self-antigen. Examples of autoimmune diseases include pemphigus vulgaris"); para [0132] "Other diseases treatable using the compositions and methods of the invention include autoimmune diseases.")

Autoantigens associated with autoimmune disease were known in the art, as evidenced by Ding, which discloses that the autoimmune disease pemphigus vulgaris (abstract) is associated with the autoantigens desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3) (p 739, right col, para 1) "autoantigens belong to the desmoglein subfamily... The PF antigen is desmoglein 1 (Dsg1) and the PV antigen is designated desmoglein 3 (Dsg3)"; abstract "More than 50% of pemphigus vulgaris sera also contain anti-desmoglein 1 autoantibodies... The anti-desmoglein 1 autoantibodies in pemphigus vulgaris induced typical pemphigus foliaceus lesions in neonatal mice... These findings suggest that the anti-desmoglein 1 antibodies in pemphigus vulgaris are pathogenic").

Further, Zimmerman discloses peptide constructs useful for treatment of an autoimmune disease such as pemphigus vulgaris (para [0039]), where the peptide construct comprises a peptide associated with autoimmune disease linked to an immune response modifying peptide (para [0040]) "Specifically, the novel peptides of this invention include peptide constructs of the following formula (I): P1-x-P2 (I) where P1 is a peptide associated with autoimmune disease... which will bind to an antigen receptor on a set or subset of T cells; P2 is an immune response modifying peptide which will (i) cause a directed immune response by said set or subset of T cells to which the peptide P1 is attached").

Given that Ding teaches autoantigen peptides associated with the autoimmune disease pemphigus vulgaris, and Powell teaches an immune response modifying peptide (CAR) that can be used to treat an autoimmune disease such as pemphigus vulgaris, one of ordinary skill in the art in view of Zimmerman would have found it obvious to link an autoantigen peptide, as taught by Ding, to an immune response modifying peptide, as taught by Powell, in order to obtain a peptide construct that can be used to treat an autoimmune disease such as pemphigus vulgaris. Thus, one of ordinary skill in the art would have found it obvious that the chimeric receptor of Powell can be a chimeric autoantibody receptor, wherein the extracellular domain comprises an autoantigen or fragment thereof. [Please note that Applicants have defined the term "chimeric autoantibody receptor" to mean a chimeric receptor that comprises an antigen for a pathogenic autoantibody, see instant specifications p 11, In 11-14 "Chimeric autoantibody receptor" or "CAAR" refers to an engineered receptor that is expressed on a T cell or any other effector cell type capable of cell-mediated cytotoxicity. The CAAR includes an antigen or fragment thereof that is specific for a pathogenic autoantibody."]

Additionally, Powell further teaches [claim 16] a vector comprising the isolated nucleic acid (para [0023]) The invention also provides a vector comprising an isolated nucleic acid sequence encoding a CAR");

Powell also teaches [claim 34] a genetically modified cell (para [0022]) The invention also provides a genetically modified T cell comprising an isolated nucleic acid sequence encoding a CAR").

As the technical features were known in the art at the time of the invention, they cannot be considered a special technical features that would otherwise unify the groups.

Groups I+ and II therefore lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Form PCT/ISA/2 10 (extra sheet) (January 2015)