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[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR ANTIGEN-SPECIFIC TOLERANCE

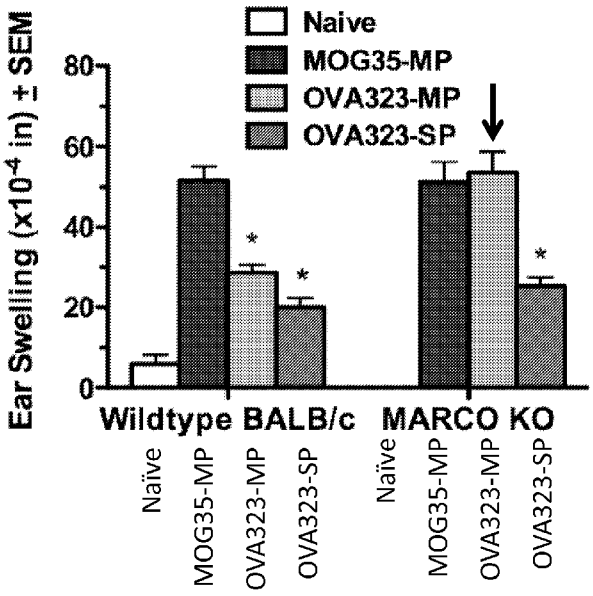

Figure 11

(57) Abstract: The present invention provides compositions and methods for inducing antigen-specific tolerance in a subject. In one embodiment, the present invention provides a composition comprising an apoptotic body and an epitope of an antigen. Also provided herein are methods of preparing and administering the composition. The composition and methods provided herein can induce antigen-specific tolerance in a subject.

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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).

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/385, 39/00, 39/38 (2013.01)
USPC - 424/193.1, 184.1, 400
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 39/385, 39/00, 39/38 (2013.01)
USPC: 424/193.1, 184.1, 400

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; PubMed; ProQuest; induce, 'antigen specific tolerance,' 'surrogate apoptotic body,' microparticle, nanoparticle, bead, 'carrier particle,' dendrimer, 'quantum dot,' liposome, 'immunodominant epitope,' 'immunodominant antigen,' 'Anergy promoting agent,' administer, subsequent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2010/085509 A1 (MILLER, S et al.) July 29, 2010; abstract; paragraphs [0005], [0006], [0007], [0008], [0012], [0013], [0014], [0018], [0019], [0020], [0023], [0025], [0026], [0029], [0033], [0035], [0036], [0045], [0047], [0075], [0085], [0090], [0094], [0099], [00100], [00102], [00105], [00108], [00122], [00125], [00126], [00149], [00200], [00201]; Claims 1, 12, 28, 37	1-21, 25-33, 61-92, 95, 96, 100, 102-111, 114, 116, 117, 120, 121 ----- 22-24, 97/92, 112, 113, 115/114/1, 115/114/20, 115/114/28, 118/1, 118/20, 118/28, 119/1, 119/20, 119/28, 122/73/1, 122/73/20, 122/73/28, 123/122/73/1, 123/122/73/20, 123/122/73/28, 124/122/73/1, 124/122/73/20, 124/122/73/28
Y	WO 2012/018380 A2 (PAULSON, JC et al.) February 9, 2012; paragraphs [0041], [0050]	22-24
Y	WO 2012/001647 A2 (HECHT, I et al.) January 5, 2012; page 3, paragraphs 4, 6	112, 113
Y	WO 2012/065153 A2 (GETTS, D et al.) May 18, 2012; paragraph [0041]	115/114/1, 115/114/20, 115/114/28, 118/1, 118/20, 118/28, 119/1, 119/20, 119/28

☒ 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 December 2013 (26.12.2013)	10 JAN 2014
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. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/031441 A1 (FITZGERALD, DJ) March 17, 2011; paragraphs [0020], [0082], [0198]	97/92, 122/73/1, 122/73/20, 122/73/28, 123/122/73/1, 123/122/73/20, 123/122/73/28, 124/122/73/1, 124/122/73/20, 124/122/73/28

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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 Supplemental Page-***-

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.:

-***-Please See Supplemental Page-***-

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.

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-***-Continuation of Box No. III: Observations Where Unity Of Invention Is Lacking:

Group I: Claims 1-33, 61/1, 61/20, 61/28, 62/1, 62/27, 62/33, 63/62/1, 63/62/27, 63/62/33, 64/63/62/1, 64/63/62/27, 64/63/62/33, 65/1, 65/20, 65/28, 66/1, 66/20, 66/28, 67/1, 67/20, 67/28, 68/1, 68/20, 68/28, 69/1, 69/20, 69/28, 70/1, 70/20, 70/28, 71/1, 71/20, 71/28, 72/1, 72/20, 72/28, 73/1, 73/20, 73/28, 74/73/1, 74/73/20, 74/73/28, 75/74/73/1, 75/74/73/20, 75/74/73/28, 76/73/1, 76/73/20, 76/73/28, 77/73/1, 77/73/20, 77/73/28, 78/77/73/1, 78/77/73/20, 78/77/73/28, 79-92, 95/92, 96/95/92, 97/92, 100/92, 102/89, 102/90, 103/102/89, 103/102/90, 104/103/102/89, 104/103/102/90, 105/79, 106/79, 107/79, 108/79, 109/79, 110/19, 111/79, 112, 113, 114/1, 114/20, 114/28, 115/114/1, 115/114/20, 115/114/28, 116/1, 116/20, 116/28, 117/116/1, 117/116/20, 117/116/28, 118/1, 118/20, 118/28, 119/1, 119/20, 119/28, 120/1, 120/20, 120/28, 121/1, 121/20, 121/28, 122/73/1, 122/73/20, 122/73/28, 123/122/73/1, 123/122/73/20, 123/122/73/28, 124/122/73/1, 124/122/73/20, 124/122/73/28; Group II: Claims 34-42, 61/34, 61/41, 62/41, 62/42, 63/62/41, 63/62/42, 65/34, 66/34, 67/34, 68/34, 69/34, 70/34, 71/34, 72/34, 73/34, 74/73/34, 75/74/73/34, 76/73/34, 77/73/34, 78/77/73/34, 114/34, 115/114/34, 116/34, 117/116/34, 118/34, 119/34, 120/34, 121/34, 122/73/34, 123/122/73/34, 124/122/73/34; Group III: Claims 43-57, 61/43, 62/43, 63/62/43, 64/63/62/43, 65/43, 65/51, 66/43, 66/51, 67/43, 67/51, 68/43, 68/51, 69/43, 69/51, 70/43, 70/51, 71/43, 71/51, 72/43, 72/51, 73/43, 73/51, 74/73/43, 74/73/51, 75/74/73/43, 75/74/73/51, 76/73/43, 76/73/51,77/73/43, 77/73/51, 78/77/73/43, 78/77/73/51, 114/43, 114/51, 115/114/43, 115/114/51, 116/43, 116/51, 117/116/43, 117/116/51, 118/43, 118/51, 119/43, 119/51, 120/43, 120/51, 121/43, 121/51, 122/73/43, 122/73/51, 123/122/73/43, 123/122/73/51, 124/122/73/43, 124/122/73/51; Group IV: Claims 58-60, 61/58, 62/58, 63/62/58, 64/63/62/58, 65/58, 66/58, 67/58, 68/58, 69/58, 70/58, 71/58, 72/58, 73/58, 74/73/58, 75/74/73/58, 76/73/58, 77/73/58, 78/77/73/58, 118/58, 119/58, 120/58, 121/58, 122/73/58, 123/122/73/58, 124/122/73/58; Group V: Claims 93, 94, 95/93, 96/95/93, 97/93, 98, 99, 100/98, 101, 102/101, 103/102/101, 104/103/102/101, 105/93, 106/93, 107/93, 108/93, 109/93, 110/93, 111/93

Group I: Claims 1-33, 61/1, 61/20, 61/28, 62/1, 62/27, 62/33, 63/62/1, 63/62/27, 63/62/33, 64/63/62/1, 64/63/62/27, 64/63/62/33, 65/1, 65/20, 65/28, 66/1, 66/20, 66/28, 67/1, 67/20, 67/28, 68/1, 68/20, 68/28, 69/1, 69/20, 69/28, 70/1, 70/20, 70/28, 71/1, 71/20, 71/28, 72/1, 72/20, 72/28, 73/1, 73/20, 73/28, 74/73/1, 74/73/20, 74/73/28, 75/74/73/1, 75/74/73/20, 75/74/73/28, 76/73/1, 76/73/20, 76/73/28, 77/73/1, 77/73/20, 77/73/28, 78/77/73/1, 78/77/73/20, 78/77/73/28, 79-92, 95/92, 96/95/92, 97/92, 100/92, 102/89, 102/90, 103/102/89, 103/102/90, 104/103/102/89, 104/103/102/90, 105/79, 106/79, 107/79, 108/79, 109/79, 110/19, 111/79, 112, 113, 114/1, 114/20, 114/28, 115/114/1, 115/114/20, 115/114/28, 116/1, 116/20, 116/28, 117/116/1, 117/116/20, 117/116/28, 118/1, 118/20, 118/28, 119/1, 119/20, 119/28, 120/1, 120/20, 120/28, 121/1, 121/20, 121/28, 122/73/1, 122/73/20, 122/73/28, 123/122/73/1, 123/122/73/20, 123/122/73/28, 124/122/73/1, 124/122/73/20 and 124/122/73/28 are directed toward a method of inducing antigen-specific tolerance in a subject suffering from or at risk of a condition comprising: administering a composition to said subject, wherein said composition comprises an apoptotic body surrogate and a plurality of immunodominant epitopes associated with one or more antigens suspected to cause said condition, and wherein said composition induces tolerance of said at least one or more antigens in said subject; a method of reducing a hypersensitivity response of a food allergy in a subject comprising: administering a composition comprising an apoptotic body surrogate and an immunodominant epitope of said food to said subject, wherein said composition induces tolerance of said food in said subject thereby reducing the hypersensitivity response of said food anergy in said subject; a method of reducing the risk of transplant rejection in a subject comprising: administering a composition comprising an apoptotic body surrogate and an immunodominant epitope of a tissue to be transplanted to said subject, wherein said composition induces tolerance of said tissue in said subject thereby reducing the risk of transplant rejection in said subject; and a composition tor induction of antigen-specific tolerance in a subject suffering from or at risk of a condition comprising: (a) an apoptotic body surrogate; and (b) a plurality of immunodominant epitopes associated with one or more antigens suspected to cause a condition, wherein said composition induces tolerance of said at least one or more antigens in said subject.

Group II: Claims 34-42, 61/34, 61/41, 62/41, 62/42, 63/62/41, 63/62/42, 65/34, 66/34, 67/34, 68/34, 69/34, 70/34, 71/34, 72/34, 73/34, 74/73/34, 75/74/73/34, 76/73/34, 77/73/34, 78/77/73/34, 114/34, 115/114/34, 116/34, 117/116/34, 118/34, 119/34, 120/34, 121/34, 122/73/34, 123/122/73/34 and 124/122/73/34 are directed toward a method of reducing a hypersensitivity response to a therapeutic in a subject comprising: administering a composition comprising an apoptotic body surrogate and an epitope of a therapeutic, wherein said composition induces tolerance of said therapeutic in said subject thereby reducing said hypersensitivity response to said therapeutic in said subject.

Group III: Claims 43-57, 61/43, 62/43, 63/62/43, 64/63/62/43, 65/43, 65/51, 66/43, 66/51, 67/43, 67/51, 68/43, 68/51, 69/43, 69/51, 70/43, 70/51, 71/43, 71/51, 72/43, 72/51, 73/43, 73/51, 74/73/43, 74/73/51, 75/74/73/43, 75/74/73/51, 76/73/43, 76/73/51,77/73/43, 77/73/51, 78/77/73/43, 78/77/73/51, 114/43, 114/51, 115/114/43, 115/114/51, 116/43, 116/51, 117/116/43, 117/116/51, 118/43, 118/51, 119/43, 119/51, 120/43, 120/51, 121/43, 121/51, 122/73/43, 122/73/51, 123/122/73/43, 123/122/73/51, 124/122/73/43 and 124/122/73/51 are directed toward a method of inducing antigen-specific tolerance in a subject suffering from or at risk of hypersensitivity to an antigen comprising: a. obtaining personalized information of a subject; b. determining from said personalized information an antigen to which said subject is hypersensitive to; and c. administering a composition comprising an apoptotic body or apoptotic body surrogate and an epitope of said antigen to said subject, thereby inducing tolerance specific to said antigen in said subject; method of inducing antigen-specific tolerance in a subject suffering from or at risk of hypersensitivity to an antigen comprising: a. obtaining a pool of immune cells from a subject; b. determining from said pool an antigen to which said subject is hypersensitive to; and c. administering a composition comprising an apoptotic body surrogate and an epitope of said antigen to said subject, thereby inducing tolerance specific to said antigen in said subject.

Group IV, Claims 58-60, 61/58, 62/58, 63/62/58, 64/63/62/58, 65/58, 66/58, 67/58, 68/58, 69/58, 70/58, 71/58, 72/58, 73/58, 74/73/58, 75/74/73/58, 76/73/58, 77/73/58, 78/77/73/58, 118/58, 119/58, 120/58, 121/58, 122/73/58, 123/122/73/58, and 124/122/73/58 are directed toward a method of delivering an antigen to a splenic marginal zone of a subject comprising: administering a composition comprising an apoptotic body surrogate and an antigen to a subject, wherein said apoptotic body surrogate is recognized by a macrophage scavenger receptor, and said macrophage scavenger receptor uptakes said antigen in said splenic marginal zone.

Group V, Claims 93, 94, 95/93, 96/95/93, 97/93, 98, 99, 100/98, 101, 102/101, 103/102/101, 104/103/102/101, 105/93, 106/93, 107/93, 108/93, 109/93, 110/93 and 111/93 are directed toward a composition for induction of antigen-specific tolerance in a subject suffering from or at risk of a condition comprising: (a) an apoptotic body surrogate; b) an epitope associated with one or more antigens suspected to cause said condition; and (c) an additional anergy promoting agent within said apoptotic body surrogate, wherein said composition induces tolerance of said antigen in said subject.

-***-Continued Within the Next Supplemental Box-***-

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-***-Continued from Previous Supplemental Box:

The inventions listed as Groups I-V 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: the special technical features of Group I include an immunodominant epitope, or a plurality of immunodominant epitopes, not present in any of Groups II-V; the special technical features of Group II include reducing a hypersensitivity response to a therapeutic in a subject comprising: administering a composition comprising an apoptotic body surrogate and an epitope of a therapeutic, wherein said composition induces tolerance of said therapeutic in said subject thereby reducing said hypersensitivity response to said therapeutic, not present in any of Groups I or III-V; the special technical features of Group III include a. obtaining personalized information of a subject; b. determining from said personalized information an antigen to which said subject is hypersensitive to, and a. obtaining a pool of immune cells from a subject; b. determining from said pool an antigen to which said subject is hypersensitive to, not present in any of Groups I, II, IV or V; the special technical features of Group IV include delivering an antigen to a splenic marginal zone of a subject comprising: administering a composition comprising an apoptotic body surrogate and an antigen to a subject, wherein said apoptotic body surrogate is recognized by a macrophage scavenger receptor, and said macrophage scavenger receptor uptakes said antigen in said splenic marginal zone, not present in any of Groups I-III or V; the special technical features of Group V include an additional anergy promoting agent within said apoptotic body surrogate, not present in any of Groups I-IV.

Groups I-V share the technical features including administering a composition comprising an apoptotic body surrogate and an antigen or epitope thereof. Groups I-III and V share the technical features including inducing tolerance. Groups I, III and V share the technical features including inducing antigen-specific tolerance in a subject suffering from or at risk of a condition. Groups I and V share the technical features including more than one antigen, and anergy. Groups I and II share the technical features including reducing a hypersensitivity response.

However, these shared technical features are previously disclosed by US 2012/0076831 A1 to Miller, et al. (hereinafter 'Miller'). Miller discloses a method of inducing antigen-specific tolerance (a method for inducing antigen-specific tolerance; paragraph [0018]) in a subject (subject; paragraph [0006]) suffering from or at risk of a condition (suffering from or at risk of autoimmune disease, transplant rejection and allergic or hyperimmune responses (a condition); paragraph [0018]) comprising: administering a composition (administering a composition; paragraphs [0007], [0019]), to said subject (subject; paragraph [0006]), wherein said composition comprises (wherein said composition comprises; paragraph [0007]) an apoptotic body surrogate (a carrier conjugated to an apoptotic signaling molecule (an apopototic body surrogate); paragraphs [0007], [0020] (see instant PCT application, paragraph [0025]), and a plurality (a plurality; paragraph [0090]) of epitopes associated with one or more antigens (antigens (epitopes associated with one or more antigens); paragraph [0090]) suspected to cause said condition (suspected to cause said condition; Claim 37), and wherein said composition induces tolerance of said at least one or more antigens (induction of antigen-specific tolerance (said composition induces tolerance of said at least one or more antigens); paragraph [0006]) in said subject (subject; paragraph [0006]), as well as reducing a hypersensitivity response (reducing hypersensitivity response; paragraph [0122]) and anergy (paragraph [0110]).

Since none of the special technical features of the Groups I-V inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Miller reference, unity of invention is lacking.