Abstract: Compositions and methods are disclosed for inhibiting the release of a proinflammatory cytokine from a vertebrate cell, and for inhibiting an inflammatory cytokine cascade in a patient. The compositions comprise, for example, high affinity antibodies that specifically bind HMGI and antigenic fragments thereof. The high affinity antibodies of the present invention and pharmaceutical compositions comprising the same are useful for many purposes, for example, as therapeutics against a wide range of inflammatory diseases and disorders such as sepsis, rheumatoid arthritis, peritonitis, Crohn’s disease, reperfusion injury, septicemia, endotoxic shock, cystic fibrosis, endocarditis, psoriasis, psoriatic arthritis, arthritis, anaphylactic shock, organ ischemia, reperfusion injury, and allograft rejection. In addition, the high affinity antibodies of the present inventions are useful as diagnostic antibodies.
Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FT, FR, GB, GR, HU, IE, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report
— with sequence listing part of description published separately in electronic form and available upon request from the International Bureau

Date of publication of the international search report: 28 August 2008
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 06/61258

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00; A61K 39/395; C07K 16/00 (2008.04)
USPC - 424/133.1; 424/146.1; 530/388.26

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 39/00; A61K 39/395; C07K 16/00 (2008.04)
USPC - 424/133.1; 424/146.1; 530/388.26

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)
PUBWEST/PGB; USPTO; EPAB; GOOGLE SCHOLAR: hmgbl, amphoteric antibody, arthritis, hyperostosis, rage, pamp, tr1, tr2, tr3, tr4, tr5, tr6, tr7, tr8, tr9, cpg, lps, peptidoglycan, bacterial adj protein, zymosan, lipoteohlic, glucan, viral ma, localization
GenCore Sequence Search: SEQ ID NOS 5 and 7

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>
</thead>
<tbody>
<tr>
<td>X - Y</td>
<td>US 2005/01 18688 A1 (Freeze et al.) 2 Jun 2005 (02.06.2005); para [0018]; [0021]; [0066] and [0250]</td>
<td>1 and 3 2</td>
</tr>
<tr>
<td>X - Y</td>
<td>KOKKOLA et al. Successful treatment of collagen-induced arthritis in mice and rats by targeting extracellular high mobility group box chromosomal protein 1 activity. Arthritis &amp; Rheumatism Jul 2003, 48(7):2052-2058; pg 2052, col 2; pg 2054 col 1; 2057 col 1 and 2; and pg 2056, Table 1</td>
<td>4-6 2</td>
</tr>
<tr>
<td>X - Y</td>
<td>DUMITRIU et al. Requirement of HMGB1 and RAGE for the maturation of human plasmacytoid dendritic cells. European Journal of Immunology May 2005, 35(7):2184 - 2190; pg 2186, col 1 and 2</td>
<td>7-14</td>
</tr>
<tr>
<td>X - Y</td>
<td>US 2006/0099207 A1 (Herrin et al.) 11 May 2006 (11.05.2006); para [0057], [0150], and SEQ ID NOS 5 and 7</td>
<td>1-14, 24 and 25</td>
</tr>
</tbody>
</table>

D. 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
06 May 2008 (06.06.2008)

Date of mailing of the international search report
24 MAY 2008

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
Lee W. Young
PCT H/PT/SC - 571-272-4300
PCT OSP - 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)
INTERNATIONAL SEARCH REPORT

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

2 | D | 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 | Lx | Claims Nos Claims 15-23, 26-33, 78, 85-93, 97-106 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

Group I (claims 1-14, 24-25) is drawn to an isolated antibody that specifically binds a human HMGB1 polypeptide or antigenic fragment thereof, wherein said antibody when administered to a subject prevents or reduces hyperostosis, the technical feature of this group is the antibody that comprises the variable region and binds the same epitope as the anti-HMGB1 antibody S2

Group II (claims 1-14, 24-25) is drawn to an isolated antibody that specifically binds a human FIMGB1 polypeptide or antigenic fragment thereof, wherein said antibody when administered to a subject prevents or reduces hyperostosis, the technical feature of this group is the antibody that comprises the variable region and binds the same epitope as the anti-HMGB1 antibody S6

| 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, where claims 24 and 25 are limited to S2

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

Group IV (claims 1-14, 24-25) is drawn to an isolated antibody that specifically binds a human HMGBI polypeptide or antigenic fragment thereof, wherein said antibody when administered to a subject prevents or reduces hyperostosis, the technical feature of this

Group is the antibody that comprises the variable region and binds the same epitope a the anti-I-IMGBI antibody G4

Group V (claims 34-37, 46-58) is drawn to a composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient wherein the HMGBI polypeptide is a full length HMGBI polypeptide of SEQ ID NO 1

Group VI (claims 34-37, 46-58) is drawn to a composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient wherein the HMGBI polypeptide is a full length HMGBI polypeptide of SEQ ID NO 2

Group VII (claims 34, 38-39, 41 ) is drawn to a composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient wherein the HMGBI polypeptide is a fragment of full length HMGBI polypeptide of SEQ ID NO 3

Group VIII (claims 34, 38, 40, 42) is drawn to a composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient wherein the I-IMGBI polypeptide is a fragment of full length HMGBI polypeptide of SEQ ID NO 4

Group IX (claims 34, 38, 40, 42) is drawn to a composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient wherein the HMGBI polypeptide is a fragment of full length HMGBI polypeptide of SEQ ID NO 28

Group X (claims 34, 38, 40, 42) is drawn to a composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient wherein the HMGBI polypeptide is a fragment of full length HMGBI polypeptide of SEQ ID NO 29

Group XI (claims 34, 38, 40, 43-45) is drawn to a composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient wherein the HMGBI polypeptide is a fragment of full length HMGBI polypeptide wherein said fragment comprises at least five, at least 10 or at least 20 contiguous amino acids

Group XII (claim 59) is drawn to a method for stimulating immune response in a patient in need thereof comprising administering the pharmaceutical composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient

Group XIII (claim 60) is drawn to a method for affecting weight loss or treating obesity in a patient in need thereof comprising administering the pharmaceutical composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient

Group XIV (claim 61) is drawn to a method of promoting tissue repair or regeneration in a patient in need thereof comprising administering the pharmaceutical composition comprising an effective amount of a combination of an HMGBI polypeptide and a TLR ligand and a pharmaceutically acceptable excipient

Group XV (claims 62-66) is drawn to a method for screening for a compound that inhibits or diminishes the specific binding of I-IMGBI to an interacting molecule (e.g a PAMP, RAGE, etc )