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(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, Twelfth Floor, Oakland, California 94607-5200 (US).

(72) Inventor; and
(71) Applicant: **MOROZ, Paul** [AU/AU]; c/o Philip Gehrig, Wrays, Level 20, 1 Castlereagh Street, Sydney, New South Wales 2000 (AU).

(72) Inventors: **YEATES, Todd**; c/o UCLA Technology Development Group, 10889 Wilshire Blvd., Suite 920, Los Angeles, California 90095-7191 (US). **MILLER, Justin**; c/o UCLA Technology Development Group, 10889 Wilshire Blvd., Suite 920, Los Angeles, California 90095-7191 (US). **CASTELLS-GRAELLS, Roger**; c/o UCLA Technology Development Group, 10889 Wilshire Blvd., Suite 920, Los Angeles, California 90095-7191 (US). **ARBING, Mark Aubrey**; c/o UCLA Technology Development Group, 10889 Wilshire Blvd., Suite 920, Los Angeles, California 90095-7191 (US). **MUNOZ, Aldo**; c/o UCLA Technology Development Group, 10889 Wilshire Blvd., Suite 920, Los Angeles, California 90095-7191 (US). **NGUYEN, Brian Thuan**; c/o UCLA Technology Development Group, 10889 Wilshire Blvd., Suite 920, Los Angeles, California 90095-7191 (US).

(74) Agent: **SUNDBY, Suzannah K.**; Canady + Lortz LLP, 1050 30th Street, NW, Washington, District of Columbia 20007 (US).

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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
13 February 2025 (13.02.2025)

(54) Title: IMMUNOSORBENT NANOPARTICLES AND METHODS OF USING THEREOF

(57) Abstract: Disclosed herein are immunosorbent nanoparticles, devices, and methods for selective removal of a target protein such as beta-2 microglobulin (B2M) from a liquid such as blood.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/033583

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 47/69*** (2024.01); ***A61M 1/16*** (2024.01); ***A61M 1/34*** (2024.01); ***B82Y 5/00*** (2024.01); ***C07K 16/28*** (2024.01); ***A61K 47/62*** (2024.01)

CPC: ***A61K 47/6929; A61K 47/62; A61M 1/16; A61M 1/3486; B82Y 5/00; C07K 16/2833***

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)

See Search History Document

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

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0020311 A1 (BOUCHER) 27 January 2011 (27.01.2011) entire document	1-6
A	US 2022/0062430 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 03 March 2022 (03.03.2022) entire document	1-6
A	US 2013/0118979 A1 (KREYMANN et al.) 16 May 2013 (16.05.2013) entire document	1-6
A	WO 1996/002278 A1 (LABORATOIRES UPSA et al.) 01 February 1996 (01.02.1996) entire document	1-6
A	US 2015/0356240 A1 (UNIVERSITY OF WASHINGTON THROUGH ITS CENTER FOR COMMERCIALIZATION) 10 December 2015 (10.12.2015) entire document	1-6

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
08 August 2024 (08.08.2024)	**13 January 2025 (13.01.2025)**

Name and mailing address of the ISA/US	Authorized officer
COMMISSIONER FOR PATENTS **MAIL STOP PCT, ATTN: ISA/US** **P.O. Box 1450** **Alexandria, VA 22313-1450** **UNITED STATES OF AMERICA**	**TAINA MATOS**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/033583

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MCNULTY et al. "Affinity Sedimentation and Magnetic Separation With Plant-Made Immunosorbent Nanoparticles for Therapeutic Protein Purification," Frontiers in Bioengineering and Biotechnology, 27 April 2022 (27.04.2022), Vol. 10, Pgs. 1-14. entire document	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/033583

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☑ forming part of the international application as filed.
   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
      ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/033583

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.: **7-11, 14-16**
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:

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 need to be paid.

Group I+: claims 1-6 are drawn to immunosorbent nanoparticles.

Group II+: claims 12 and 13 are drawn to hemodialysis devices.

The first invention of Group I+ is restricted to immunosorbent nanoparticles comprising subunit proteins comprising SEQ ID NOs: 1 and 2, and protein chains comprising SEQ ID NOs: 42 and 43. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed compound species presented in the claims (subunit protein—claim 4; protein chains—claim 5). It is believed that claims 1-6 read on this first named invention and thus these claims will be searched without fee to the extent that they read on immunosorbent nanoparticles comprising subunit proteins comprising SEQ ID NOs: 1 and 2, and protein chains comprising SEQ ID NOs: 42 and 43.

An exemplary election of Group II+ is a hemodialysis device comprising a plurality of self-assembling protein cages comprising subunit proteins comprising SEQ ID NOs: 1 and 2.

Applicant is invited to elect additional immunosorbent nanoparticles comprising subunit proteins and protein chains, and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying an additional fee for each election. An exemplary election would be immunosorbent nanoparticles comprising subunit proteins comprising SEQ ID NOs: 3 and 4, and protein chains comprising SEQ ID NOs: 42 and 43. Additional immunosorbent nanoparticles and their respective, corresponding, SEQ ID NOs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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/ examined.

The inventions listed in Groups I+ 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:

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

The Groups I+ and II+ formulas do not share a significant structural element responsible for forming protein subunits requiring the selection of alternative amino acid sequences "wherein the one or more subunit proteins are selected from the group consisting of: a) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 1, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 2; b) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 3, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 4; c) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 5, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 6; d) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 7, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 8; 34 e) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 9 9%, or 100% sequence identity to SEQ ID NO: 9, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 10; f) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 11, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 12; g) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 13, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 14; h) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 15, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 16; i) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 17, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 18; j) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 19, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 20; k) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 21, and a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 22; 1) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 23; and m) a subunit protein having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 9 8%, 99%, or 100% sequence identity to SEQ ID NO: 24."

The special technical features of Group I+, immunosorbent nanoparticles, are not present in Group II+; and the special technical features of Group II+, hemodialysis devices, are not present in Group I+.

Additionally, even if Groups I+ and II+ were considered to share the technical features of an immunosorbent nanoparticle comprising or consisting of (a) a plurality of one or more subunit proteins which form a protein cage having an exterior surface, and (b) a binder against beta-2 microglobulin (B2M), said binder is recombinantly linked, directly or indirectly, to at least one of the one or more subunit proteins, wherein the binder is presented on the exterior surface; and A hemodialysis device comprising (a) a dialyzer, and (b) an article comprising a housing having at least one outlet, and (b) a plurality of self-assembling protein cages contained within the housing, these shared technical features do not represent a contribution over the prior art.

Specifically, "Affinity Sedimentation and Magnetic Separation With Plant-Made Immunosorbent Nanoparticles for Therapeutic Protein Purification," to McNulty et al. teaches immunosorbent nanoparticles (virus-based immunosorbent nanoparticle, Abstract).

Further, US 2022/0062430 A1 to The Regents Of The University Of California teaches nanoparticles (The field of the invention generally relates to Self-Assembling Protein Nanoparticles (SAPN) and their use as carrier molecules for passenger molecules of interest, Para. [0003]) comprising or consisting of (a) a plurality of one or more subunit proteins which form a protein cage having an exterior surface, and (b) a binder, said binder is recombinantly linked, directly or indirectly, to at least one of the one or more subunit proteins, wherein the binder is presented on the exterior surface (he present invention provides for a protein cage polypeptide (or scaffolding protein) useful or capable of forming a hollow tetrahedral pyramid structure, wherein the protein cage polypeptide (i.e., the scaffolding protein or a passenger peptide covalently linked thereto is capable of binding specifically to an antibody or part thereof, or any chimeric protein, molecule or compound comprising

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

the antibody, or part thereof, Para. [0025]; PCs with a variety of antibodies can be mixed to create a SAPNA with a diverse set of antibodies on its surface, Para. [0044]).

Further, WO 1996/002278 A1 to Laboratoires Upsa et al. teaches a binder against beta-2 microglobulin (B2M) (Immunonanoparticles consisting of nanoparticles of a polymeric methylidenemalonate compound coated with anti- beta 2 microglobulin antibodies, Abstract).

Further, US 2013/0118979 A1 to Kreymann et al. teaches a hemodialysis device comprising (a) a dialyzer, and (b) an article comprising a housing having at least one outlet, and (b) a plurality of nanoparticles contained within the housing (FIG. 1 shows a schematic block diagram of a dialysis system according to an embodiment of the present invention. Via an arterial blood line 1, blood from a patient is supplied to a dialyzer 2. Before the blood is supplied to the dialyzer 2, a predilution fluid 3 is added to the blood. In the dialyzer 2, the respective flows of blood and dialysate may be conducted in concurrent flow, as shown in FIG. 1, Para. [0054]; FIG. 1 discloses a device comprising a housing and an outlet; The toxin is removed by e.g. a precipitation reaction or by the detoxification unit as such, e.g. by diafiltration (s. above). Examples for carrier substances exhibiting the property of (reversibly) binding (dependent on the physico-chemical properties) to a specific toxin may be selected according to the character of the toxin to be bound. In general,… nanoparticles,… exhibiting this property., Para. [0029]).

The inventions listed in Groups I+ and II+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

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.: **1-6**

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.