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(71) Applicant: **THE SCRIPPS RESEARCH INSTITUTE**
[US/US]; 10550 North Torrey Pines Road, La Jolla, CA
92037 (US).

(72) Inventor: **GARABEDIAN, Brett**; 526 Camino Del Mar,
Apt. 28, Del Mar, CA 92014 (US).

(74) Agent: **FITTING, Thomas** et al.; The Scripps Research In-
stitute, 10550 North Torrey Pines Road, Mail Drop Tpc-8,
La Jolla, CA 92037 (US).

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(54) Title: SHEDDASE-TARGETING CHIMERAS FOR PROTEOSTASIS MODULATION

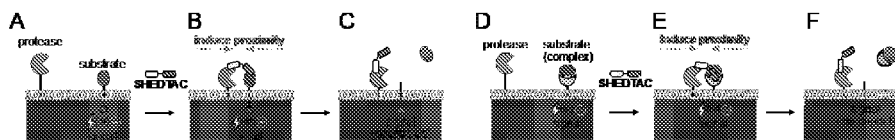


FIG. 1

(57) Abstract: The invention provides fusion molecules for inducing proximity between integral membrane proteins and integral membrane proteases (sheddas), thereby promoting targeted proteolysis (shedding) of the target membrane protein ectodomain. These fusion molecules, Sheddase-Targeting Chimera (SHEDTACs), contain a protease-targeting domain and a substrate-targeting domain that respectively bind to a sheddase and a target protein of interest (e.g., a cell surface receptor). Also provided in the invention are polynucleotides encoding the fusion molecules, related expression vectors and host cells, as well as methods using the fusion molecules to accelerate integral membrane proteolysis by local sheddas.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/048537

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 13ter.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:

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 1-18 are drawn to fusion molecules, polynucleotides, vectors, cells, and pharmaceutical compositions.

Group II: claims 19-24 are drawn to methods.

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:

The special technical features of Group I, fusion molecules, polynucleotides, vectors, cells, and pharmaceutical compositions, are not present in Group II; the special technical features of Group II, methods, are not present in Group I.

Additionally, even if Groups I and II were considered to share the technical features of a fusion molecule that comprises a protease-targeting domain and a covalently linked substrate-targeting domain, and the protease-targeting domain specifically binds to an integral membrane protease or an auxiliary membrane protein in a multimeric integral membrane protease complex, and wherein the integral membrane protease can cleave the extracellular domain, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2008/074840 A2 to Ablynx N.V. (hereinafter, "Ablynx").

Ablynx teaches a fusion molecule that comprises a protease-targeting domain and a covalently linked substrate-targeting domain (Another multispecific polypeptide of the invention may at least comprise at least one amino acid sequence against an ADAM proteinase and at least one binding unit against a receptor so as to induce shedding and inactivation of said receptor... a multispecific polypeptide of the invention may at least comprise at least one amino acid sequence against an ADAM proteinase and at least one binding unit against a TNF receptor; page 78, lines 25-33; functional groups may be covalently linked to a nanobody; page 139, lines 19-33), and the protease-targeting domain specifically binds to an integral membrane protease or an auxiliary membrane protein in a multimeric integral membrane protease complex (a multispecific polypeptide of the invention may at least comprise at least one amino acid sequence against an ADAM proteinase; page 78, lines 25-33), and wherein the integral membrane protease can cleave the extracellular domain (ADAM-mediated ectodomain-shedding, i.e. the ADAM-mediated release of extracellular domains from the substrate; page 5, lines 17-25).

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 feature.

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first 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.: **1-18**

- 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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/048537

| A. CLASSIFICATION OF SUBJECT MATTER | | |
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| IPC: C07K 16/40 (2025.01); C12N 15/79 (2025.01); A61K 39/395 (2025.01); C07K 16/28 (2025.01); C12N 5/10 (2025.01) CPC: C07K 16/40 ; C07K 16/28 ; A61K 39/395 ; C12N 15/79 ; C07K 2317/75 ; C07K 2317/569 ; C12N 5/10 | | |
| 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. |
| X | WO 2008/074840 A2 (ABLYNX N.V.) 26 June 2008 (26.06.2008) entire document | 1-10, 13-18 |
| Y | entire document | 11, 12 |
| Y | WO 2019/179365 A1 (WUXI BIOLOGICS IRELAND LIMITED et al.) 26 September 2019 (26.09.2019) entire document | 11, 12 |
| A | JIA et al., ADAM17 A Molecular Switch to Control TNFR2 During Atherogenesis In Vivo, Arterioscler Thromb Vasc Biol., Vol. 37, 2017, Pgs. 176-178 entire document | 1-18 |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex. | | |
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| Name and mailing address of the ISA/US COMMISSIONER FOR PATENTS MAIL STOP PCT, ATTN: ISA/US P.O. Box 1450 Alexandria, VA 22313-1450 UNITED STATES OF AMERICA | | Authorized officer TAINA MATOS |
| Facsimile No. 571-273-8300 | | Telephone No. 571-272-4300 |