(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 December 2015 (03.12.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/183995 A3

(51) International Patent Classification:
*A61K 38/07* (2006.01) *A61K 31/353* (2006.01)

(21) International Application Number:
PCT/US2015/032728

(22) International Filing Date:
27 May 2015 (27.05.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/003,844 28 May 2014 (28.05.2014) US

(71) Applicant: **STEALTH PEPTIDES INTERNATIONAL, INC.** [—/MC]; 2nd Floor, Le Prince de Galles, 3-5 Avenue des Citronniers, 98000 Monaco (MC).

(72) Inventor; and
(71) Applicant : **WILSON, D. Travis** [US/US]; 22 Brewster Road, Newton, Massachusetts 02461 (US).

(74) Agents: **VAVRA, Stephanie H.** et al.; Foley & Lardner LLP, 3000 K Street N.W., Suite 600, Washington, District of Columbia 20007-5109 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, 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).

**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**:

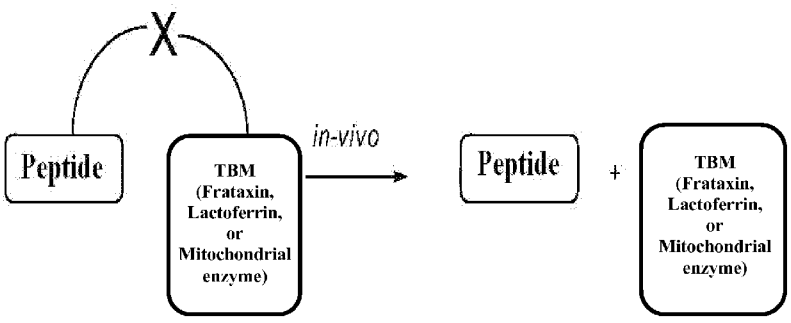
— *with international search report (Art. 21(3))*

— *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))*

*[Continued on next page]*

(54) Title: THERAPEUTIC COMPOSITIONS INCLUDING FRATAXIN, LACTOFERRIN, AND MITOCHONDRIAL ENERGY GENERATING ENZYMES, AND USES THEREOF

**FIG. 1**




(57) Abstract: Disclosed herein are methods and compositions for the treatment and/or prevention of diseases or conditions comprising administration of a therapeutic biological molecule, and/or naturally or artificially occurring derivatives, analogues, or pharmaceutically acceptable salts thereof, alone or in combination with one or more active agents (*e.g.*, an aromatic-cationic peptide). The present technology provides compositions related to aromatic-cationic peptides linked to a therapeutic biological molecule and uses of the same. In some embodiments, the aromatic-cationic peptide comprises 2',6'-dimethyl-Tyr-D-Arg-Phe-Lys-$NH_2$, Phe-D-Arg-Phe-Lys-$NH_2$, or D-Arg-2',6'-Dmt-Lys-Phe-$NH_2$.

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**(88) Date of publication of the international search report**:
21 January 2016

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/32728

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/07, 31/353 (2015.01)
CPC - A61K 38/07, 38/00, 31/353
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): C07K 16/00; C12P 21/08; A61K 38/07, 31/353 (2015.01)
CPC: A61K 47/48476, 38/07, 38/00, 31/353; C07K 2317/24; USPC: 530/391.1, 387.1, 391.7, 391.1, 386, 380, 350; 514/1.1, 1

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google; Google Scholar; PubMed; Dialog ProQuest; frataxin, 'aromatic-cationic peptide,' '2'6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2'

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2013/0303436 A1 (STEALTH PEPTIDES INTERNATIOANL, INC.) November 14, 2013; abstract; paragraph [0009], [0078] | 1-6, 8-25 |
| Y | US 2011/0245146 A1 (PAYNE, RM) October 6, 2011; paragraphs [0009], [0031] | 1-6, 8-25 |

☐ 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
"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 |
|---|---|
| 15 October 2015 (15.10.2015) | 13 NOV 2015 |
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (January 2015)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/32728

**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
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.

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/US15/32728

-***-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.

Groups I+: Claims 1-6 and 8-25 are directed toward a composition comprising a therapeutic biological molecule as described in Section I in combination with one or more aromatic-cationic peptides disclosed in Section II; and methods associated with said composition.

The composition and methods will be searched to the extent that the therapeutic biological molecule encompasses frataxin and the aromatic-cationic peptide encompasses 2',6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2. It is believed that Claims 1 (in-part), 2 (in-part), 3 (in-part), 4 (in-part), 5 (in-part), 6 (in-part), 8 (in-part), 9 (in-part), 10 (in-part), 11 (in-part), 12 (in-part), 13 (in-part), 14 (in-part), 15 (in-part), 16 (in-part), 17 (in-part), 18 (in-part), 19 (in-part), 20 (in-part), 21 (in-part), 22 (in-part), 23 (in-part), 24 (in-part) and 25 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass frataxin and 2'6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2. 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. An Exemplary Election would be: lactoferrin and D-Arg-2',6'-Dmt-Lys-PheNH2.

Groups II+: Claims 26-58 are directed toward a peptide conjugate comprising a therapeutic biological molecule conjugated to an aromatic-cationic peptide, wherein the aromatic-cationic peptide is selected from the group consisting of: 2',6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2, Phe-D-Arg-Phe-LysNH2, D-Arg-2',6' -Dmt-Lys-Phe-NH2, and a peptide of Table A, Table 5, Table 6 or Table 7; and wherein the therapeutic biological molecule is a compound described in Section I; and methods associated with said conjugate.

The conjugate and methods can be searched to the extent that the therapeutic biological molecule encompasses frataxin and the aromatic-cationic peptide encompasses 2',6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2. It is believed that Claims 26 (in-part), 27 (in-part), 28 (in-part), 29 (in-part), 30 (in-part), 32(in-part), 33 (in-part), 34 (in-part), 35 (in-part), 36 (in-part), 37 (in-part), 38 (in-part), 39 (in-part), 40 (in-part), 41 (in-part), 42 (in-part), 43 (in-part), 44 (in-part), 45 (in-part), 46 (in-part), 47 (in-part), 48 (in-part), 49 (in-part), 50 (in-part), 51 (in-part), 52 (in-part), 53 (in-part), 54 (in-part), 55 (in-part), 56 (in-part); 57 (in-part) and 58 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass frataxin and 2'6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2. 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. An Exemplary Election would be: lactoferrin and D-Arg-2',6'-Dmt-Lys-PheNH2.

The inventions listed as Groups I+-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 Groups I + include cyclosporine, which is not present in Groups II+, the special technical features of Groups II+ including a conjugate, which is not present in Groups I+.

Groups I+-II+ share the technical features including a composition comprising a therapeutic biological molecule as described in Section I in combination with one or more aromatic-cationic peptides selected from the group consisting of: 2',6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2; Phe-D-Arg-Phe-LysNH2, D-Arg-2',6' -Dmt-Lys-Phe-NH2, and a peptide of Table A, Table 5, Table 6 or Table 7; methods including: a) a method for treating or preventing a disease or condition; b) a method for reducing CD36 expression in a subject in need thereof; c) a method for treating or preventing a disease or condition characterized by CD36 elevation in a subject in need thereof; d) a method for reducing oxidative damage in a removed organ or tissue; e) a method for preventing the loss of dopamine-producing neurons in a subject in need thereof; f) a method of reducing oxidative damage associated with a neurodegenerative disease in a subject in need thereof; g) a method for preventing or treating a burn injury in a subject in need thereof; h) a method for treating or preventing mechanical ventilation-induced diaphragm dysfunction in a subject in need thereof; i) a method for treating or preventing no reflow following ischemia-reperfusion injury in a subject in need thereof; k) a method for preventing norepinephrine uptake in a subject in need of analgesia; l) a method for treating or preventing drug-induced peripheral neuropathy or hyperalgesia in a subject in need thereof; m) a method for inhibiting or suppressing pain in a subject in need thereof; and n) a method for treating atherosclerotic renal vascular disease (ARVD) in a subject in need thereof; said methods comprising administering a therapeutically effective amount of a composition comprising a therapeutic biological molecule as described in Section I, in combination with one or more aromatic-cationic peptides selected from the group consisting of: 2',6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2, Phe-D-Arg-Phe-LysNH2, D-Arg-2',6' -Dmt-Lys-Phe-NH2, and a peptide of Table A, Table 5, Table 6 or Table 7.

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Groups I+ share the technical features including a composition comprising a therapeutic biological molecule as described in Section I in combination with one or more aromatic-cationic peptides disclosed in Section II; methods including: a) a method for treating or preventing a disease or condition; b) a method for reducing CD36 expression in a subject in need thereof; c) a method for treating or preventing a disease or condition characterized by CD36 elevation in a subject in need thereof; d) a method for reducing oxidative damage in a removed organ or tissue; e) a method for preventing the loss of dopamine-producing neurons in a subject in need thereof; f) a method of reducing oxidative damage associated with a neurodegenerative disease in a subject in need thereof; g) a method for preventing or treating a burn injury in a subject in need thereof; h) a method for treating or preventing mechanical ventilation-induced diaphragm dysfunction in a subject in need thereof; i) a method for treating or preventing no reflow following ischemia-reperfusion injury in a subject in need thereof; k) a method for preventing norepinephrine uptake in a subject in need of analgesia; l) a method for treating or preventing drug-induced peripheral neuropathy or hyperalgesia in a subject in need thereof; m) a method for inhibiting or suppressing pain in a subject in need thereof; and n) a method for treating atherosclerotic renal vascular disease (ARVD) in a subject in need thereof; said methods comprising administering a therapeutically effective amount of a composition comprising a therapeutic biological molecule as described in Section I, in combination with one or more aromatic-cationic peptides disclosed in Section II, and optionally one or more additional active agents such as cyclosporine, a cardiac drug, an anti-inflammatory, an anti-hypertensive drug, an antibody, an ophthalmic drug, an antioxidant, a metal complexer, and an antihistamine.

Groups II+ share the technical features including: a peptide conjugate comprising a therapeutic biological molecule conjugated to an aromatic-cationic peptide, wherein the aromatic-cationic peptide is selected from the group consisting of: 2',6'-dimethyl-Tyr-D-Arg-Phe-Lys-NH2, Phe-D-Arg-Phe-LysNH2, D-Arg-2',6' -Dmt-Lys-Phe-NH2, and a peptide of Table A, Table 5, Table 6 or Table 7; and wherein the therapeutic biological molecule is a compound described in Section I; methods including: a) a method for treating or preventing a disease or condition; b) a method for reducing CD36 expression in a subject in need thereof; c) a method for treating or preventing a disease or condition characterized by CD36 elevation in a subject in need thereof; d) a method for reducing oxidative damage in a removed organ or tissue; e) a method for preventing the loss of dopamine-producing neurons in a subject in need thereof; f) a method of reducing oxidative damage associated with a neurodegenerative disease in a subject in need thereof; g) a method for preventing or treating a burn injury in a subject in need thereof; h) a method for treating or preventing mechanical ventilation-induced diaphragm dysfunction in a subject in need thereof; i) a method for treating or preventing no reflow following ischemia-reperfusion injury in a subject in need thereof; k) a method for preventing norepinephrine uptake in a subject in need of analgesia; l) a method for treating or preventing drug-induced peripheral neuropathy or hyperalgesia in a subject in need thereof; m) a method for inhibiting or suppressing pain in a subject in need thereof; and n) a method for treating atherosclerotic renal vascular disease (ARVD) in a subject in need thereof; said methods comprising administering a therapeutically effective amount of the conjugate; and a method for delivering an aromatic-cationic peptide and/or a therapeutic biological molecule to a cell, the method comprising contacting the cell with a peptide conjugate, wherein the peptide conjugate comprises the therapeutic biological molecule conjugated to an aromatic-cationic peptide, wherein the aromatic-cationic peptide is selected from the group consisting of: 2',6'-dimethyl-Tyr-D-Arg-Phe-LysNH2, Phe-D-Arg-Phe-Lys-NH2, D-Arg-2',6' -Dmt-Lys-Phe-NH2, and a peptide of Table A, Table 5, Table 6 or Table 7; and wherein the therapeutic biological molecule is a compound described in Section I.

-***-Continued on Next Supplemental Page-***-

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However, these shared technical features are previously disclosed by US 2013/0303436 A1 (STEALTH PEPTIDES, INC.) (hereinafter 'Stealth Peptides') in view of US 2011/0245146 A1 (PAYNE).

Stealth Peptides discloses a composition comprising a combination (a composition comprising a combination; paragraph [0009]) with one or more aromatic-cationic peptides including D-Arg-2',6'-Dmt-Lys-Phe-NH2 (with one or more aromatic-cationic peptides including D-Arg-2',6'-Dmt-Lys-Phe-NH2; paragraph [0009]); and methods including: a) a method for treating or preventing a disease or condition (a method for treating or preventing a disease or condition; paragraph [0012]); b) a method for reducing CD36 expression in a subject in need thereof (a method for reducing CD36 expression in a subject in need thereof; paragraph [0017]); c) a method for treating or preventing a disease or condition characterized by CD36 elevation in a subject in need thereof (a method for treating or preventing a disease or condition characterized by CD36 elevation in a subject in need thereof; paragraph [0018]); d) a method for reducing oxidative damage in a removed organ or tissue (a method for reducing oxidative damage in a removed organ or tissue; paragraph [0020]); e) a method for preventing the loss of dopamine-producing neurons in a subject in need thereof (a method for preventing the loss of dopamine-producing neurons in a subject in need thereof; paragraph [0022]); f) a method of reducing oxidative damage associated with a neurodegenerative disease in a subject in need thereof (a method of reducing oxidative damage associated with a neurodegenerative disease in a subject in need thereof; paragraph [0024]); g) a method for preventing or treating a burn injury in a subject in need thereof (a method for preventing or treating a burn injury in a subject in need thereof; paragraph [0026]); h) a method for treating or preventing mechanical ventilation-induced diaphragm dysfunction in a subject in need thereof (a method for treating or preventing mechanical ventilation-induced diaphragm dysfunction in a subject in need thereof; paragraph [0027]); i) a method for treating or preventing no reflow following ischemia-reperfusion injury in a subject in need thereof (a method for treating or preventing no reflow following ischemia-reperfusion injury in a subject in need thereof; paragraph [0028]); k) a method for preventing norepinephrine uptake in a subject in need of analgesia (a method for preventing norepinephrine uptake in a subject in need of analgesia; paragraph [0029]); l) a method for treating or preventing drug-induced peripheral neuropathy or hyperalgesia in a subject in need thereof (a method for treating or preventing drug-induced peripheral neuropathy or hyperalgesia in a subject in need thereof; paragraph [0030]); m) a method for inhibiting or suppressing pain in a subject in need thereof (a method for inhibiting or suppressing pain in a subject in need thereof; paragraph [0031]); and n) a method for treating atherosclerotic renal vascular disease (ARVD) in a subject in need thereof (a method for treating atherosclerotic renal vascular disease (ARVD) in a subject in need thereof; paragraph [0032]); said methods comprising administering a therapeutically effective amount of a composition (comprising administering a therapeutically effective amount of a composition; paragraph [0012]) comprising a combination (comprising a combination; paragraph [0009]) with one or more aromatic-cationic including D-Arg-2',6'-Dmt-Lys-Phe-NH2 (with one or more aromatic-cationic including D-Arg-2',6'-Dmt-Lys-Phe-NH2; paragraph [0009]); optionally further comprising one or more additional active agents (optionally further comprising one or more additional active agents; paragraph [0010]) such as a cardiac drug, an anti-inflammatory, an anti-hypertensive drug, an ophthalmic drug, and an antioxidant (such as a cardiac drug, an anti-inflammatory, an anti-hypertensive drug, an ophthalmic drug, and an antioxidant; paragraph [0010]); and a method for delivering an aromatic-cationic peptide to a cell (a method for contacting a cell with an aromatic-cationic peptide (a method for delivering an aromatic-cationic peptide to a cell); paragraph [0310]), the method comprising contacting the cell with a peptide (method comprising contacting the cell with a peptide; paragraph [0310]), wherein the peptide comprises an aromatic-cationic peptide (wherein the peptide comprises an aromatic-cationic peptide; paragraph [0310]), wherein the aromatic-cationic peptide is D-Arg-2',6'-Dmt-Lys-Phe-NH2 (wherein the aromatic-cationic peptide is D-Arg-2',6'-Dmt-Lys-Phe-NH2; paragraph [0310]). Stealth further discloses treating or preventing mitochondrial dysfunction in a subject (treating or preventing mitochondrial dysfunction in a subject; paragraph [0012]) comprising administering a therapeutically effective amount of the composition (comprising administering a therapeutically effective amount of the composition; paragraph [0012]).

Stealth Peptides does not disclose frataxin; and a peptide conjugate comprising frataxin.

Payne discloses frataxin (frataxin; paragraph [0031]); and a peptide conjugate comprising frataxin (a tat-frataxin fusion protein (a peptide conjugate comprising frataxin); paragraph [0031]) for delivery to mitochondria (for delivery to mitochondria; abstract).

It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Stealth Peptides, for including the use of a composition comprising frataxin and a cationic-aromatic peptide or a conjugate thereof, for delivery to mitochondria, as previously disclosed by Payne, for providing methods of treating or preventing mitochondrial dysfunction, as previously disclosed by Stealth Peptides, wherein said composition would have been useful in treating mitochondrial dysfunctions associated with low levels of frataxin, such as Freidreich's ataxia.

Since none of the special technical features of the Groups I+-II+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Stealth Peptides and Payne references, unity of invention is lacking.