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61/296,339 19 January 2010 (19.01.2010) US(71) Applicant (for all designated States except US): **THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK** [US/US]; 535 West 116th Street, New York, NY 10027 (US).

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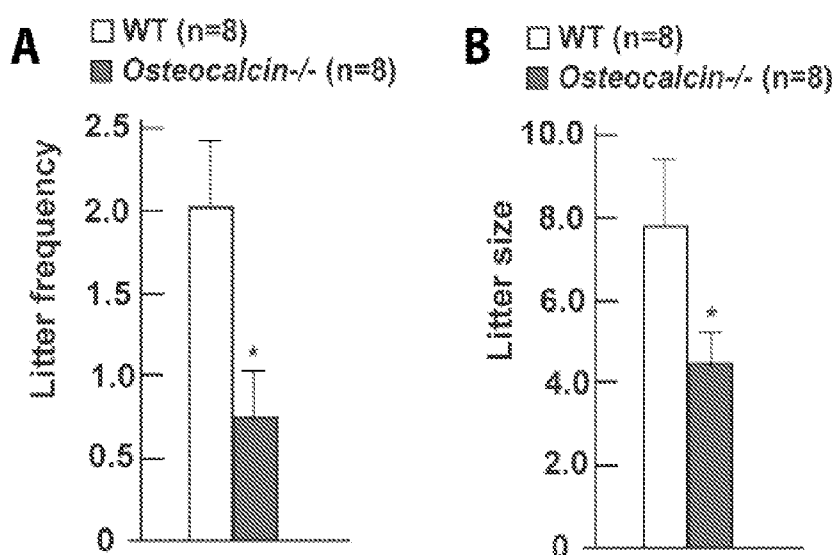
— with international search report (Art. 21(3))

— with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:
27 March 2014

(54) Title: OSTEOCALCIN AS A TREATMENT FOR MALE REPRODUCTIVE DISORDERS

FIGURE 1



(57) Abstract: Methods and compositions for treating, preventing, or diagnosing disorders related to reproduction in male mammals, preferably humans, are provided. The methods generally involve modulation of the OST-PTP signaling pathway or the PTP-IB signaling pathway involving gamma-carboxylase and osteocalcin. Disorders amenable to treatment by the methods include, but are not limited to, male infertility, low sperm count, impaired sperm motility, impaired sperm viability, low testosterone levels, reduced libido, erectile dysfunction, underdevelopment of testes, and excess apoptosis in testes.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/21634

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 filed or furnished:

a. (means)



on paper



in electronic form

b. (time)



in the international application as filed



together with the international application in electronic form



subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore ver 6.3 SEQ ID NOs: 2, 12, 13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/21634

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.: 4, 5, 19-24, 32, 36-38, 44 and 45
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 must be paid.

Group I: Claims 1-3 and 6-11, directed to a method treating disorders related to reproduction in male mammals comprising administering to a male mammal a pharmaceutical composition comprising a therapeutically effective amount of uncarboxylated osteocalcin and a carrier or excipient.

Group II: claims 12-18, 25-28, 33-35, 39-43 and 46-48, directed to a method of treating disorders in reproduction in male mammals comprising administering a pharmaceutical composition comprising an agent that modulates OST-PTP expression, activity or the OST-PTP signaling pathway.

-----continued on Extra 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.:
Claims 1-3 and 6-11

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/US 11/21634

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/00 (2011.01)

USPC - 514/1.1

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)
USPC: 514/1.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/1.1 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PubWEST (PGPB, EPAB, JPAB, USPT); Google Scholar; GenCore sequence search (AA)
Search terms: Osteocalcin (synonyms: BGP, Bone Gla protein, BGLAP), undercarboxylated or uncarboxylated, Glu residues at positions 17, 21, 24, sperm motility, sperm viability, reproductive disorder, adminst\$6, pharmaceutically acceptable carrier

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/033518 A2 (KARSENTY et al.) 20 March 2008 (20.03.2008). Especially para [0002], [0007], [0011], [0012], [0019], [0020]-[0023], [0075]-[0077], [0178], [0264], claim 20.	1-3, 6-11
Y	MAURO et al. Identification of a hormonally regulated protein tyrosine phosphatase associated with bone and testicular differentiation. J Biol Chem. 02 December 1994, Vol 269, No 48, Pages 30659-30667. Especially abstract; pg 30665, col 2, para 1; pg 30667 col 1 para 2.	1-3, 6-11
Y	COMHAIRE et al. Mechanisms and effects of male genital tract infection on sperm quality and fertilizing potential: the andrologist's viewpoint. Hum Reprod Update. September-October 1999 Vol 5, No 5, Pages 393-398. Especially abstract.	1-3, 6-11
Y	US 2004/0082018 A1 (EKEMA et al.) 29 April 2004 (20.04.2004). Especially para [0005], [0031].	1-3, 6-11

☐ 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

18 August 2011 (18.08.2011)

Date of mailing of the international search report

30 AUG 2011

Name and mailing address of the ISA/US

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P.O. Box 1450, Alexandria, Virginia 22313-1450

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/21634

Continuation of Box III (Lack of Unity of Invention)

Group III: claims 29-31, directed to a method of diagnosing a patient as being at risk of or having a disorder related to reproduction, comprising: i) determining the ratio of uncarboxylated osteocalcin to total osteocalcin; and ii) comparing the ratio to a standard or reference ratio.

Group IV: claims 49 and 50, directed to a method of contraception for use in male mammals comprising administering to a male mammal a therapeutically effective amount of an antagonist of uncarboxylated osteocalcin and a carrier or excipient.

The inventions listed as Groups I - IV 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 feature of the Group IV claims is a method of contraception - not required by the claims of any other Group. The special technical feature of the Group III claims is a method of diagnosing a patient as being at risk of or having a disorder related to reproduction - not required by the claims of any other Group. The special technical feature of the Group II claims is a method of treating disorders in reproduction in male mammals comprising administering a pharmaceutical composition comprising an agent that modulates OST-PTP expression or activity - not required by the claims of any other Group.

The only common technical element shared by the above groups is that they are related to fertility in male mammals. Groups I, III and IV share a common technical element of being related to undercarboxylated osteocalcin. This common technical element does not represent an improvement over the prior art of the article entitled "The physiology of vitamin K nutriture and vitamin K-dependent protein function in atherosclerosis" by Berkner et al., which discloses wherein undercarboxylation of osteocalcin in mammals was known ("The appreciation that vitamin K also supports non-hemostatic function has led to the development of assays that measure osteocalcin carboxylation, which are based on binding of osteocalcin to either hydroxyapatite or to antibodies that recognize the extent of osteocalcin carboxylation. Studies with such assays show that while defective hemostasis is rarely detected in the normal population, undercarboxylation of osteocalcin is common" - pg. 2124, col 2, para 3). A further common technical element shared by Groups I, III and IV is the relation of osteocalcin to infertility in males. This common technical element does not improve upon the prior art of US 2004/0082018 A1 to Ekema et al., which discloses uses for osteocalcin or nucleic acids encoding osteocalcin (abstract), wherein disorders of osteocalcin affect sperm motility and viability (para [0005]), and the administration of osteocalcin for treatment of disorders of sperm motility (para [0031]). Further, Ekema discloses wherein "variants can affect the function of one or more of gamma-carboxyglutamic acid residues" (para [0071]), and wherein the modification may comprise "Blockage of the amino or carboxyl group in a polypeptide" (para [0096]). Although Ekema does not explicitly disclose wherein the administration is to a male mammal in need of treatment for a reproductive disorder, or wherein the composition administered includes a carrier or excipient, it would have been obvious to a person skilled in the art, based on the teaching of Ekema, that treatment of a disorders of sperm motility would have included people in need of treatment for a reproductive disorder, it further would have been obvious to a skilled practitioner that the subject of treatment would have been a male mammal, as Ekema deals with sperm motility, and sperm was known to be the male gamete. Further, the use of carriers and excipients was common in the art for the administration of peptides or other protein expression modulators, such as inhibitory RNA molecules, and would have been obvious to a person of skill in the art. Further, as Ekema teaches wherein osteocalcin is typically carboxylated on residues 17, 21, and 24, (para [0029]), it would have been obvious to a person skilled in the art that the blockage taught by Ekema would have been targeted to these residues. Therefore, the inventions of Groups I - IV lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Continuation of Section 4:

Claims 4, 5, 19-24, 32, 36-38, 44 and 45 are not formed according to the second and third sentences of Rule 6.4(a) regarding multiply dependent claims.