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ning of each regular issue of the PCT Gazette.*

(54) Title: HBM VARIANTS THAT MODULATE BONE MASS AND LIPID LEVELS

(57) Abstract: The present invention relates to methods and materials used to express an HBM-like polypeptide derived from HBM, LRP5 or LRP6 in animal cells and transgenic animals. The present invention also relates to transgenic animals expressing the HBM-like polypeptides. The invention provides nucleic acids, including coding sequences, oligonucleotide primers and probes, proteins, cloning vectors, expression vectors, transformed hosts, methods of developing pharmaceutical compositions, methods of identifying molecules involved in bone development, and methods of diagnosing and treating diseases involved in bone development and lipid modulation. In preferred embodiments, the present invention is directed to methods for treating, diagnosing and preventing osteoporosis.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/14877

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 14/435; C12N 15/12; G01N 33/48

US CL : 536/23.1, 23.5; 530/350; 435/6

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)

U.S. : 536/23.1, 23.5; 530/350; 435/6

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)
DIALOG (Biotech Files); GenEMBL sequence databases; EAST (U.S. Patents and PGPubs, DERWENT)**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GONG, Y. et al. LDL-Receptor-Related Protein 5 (LRP5) Affects Bone Accrual and Eye Development. Cell. 16 November 2001, Vol. 107, pages 513-523, see entire document.	1-7, 18, 19, 45
A	JOHNSON, M.L. et al. Linkage of a Gene Causing High Bone Mass to Human Chromosome 11 (11q12-13). Am. J. Hum. Genet. 1997, Vol. 60, pages 1326-1332, see entire document.	1-7, 18, 19, 45
A	MAGOORI, K. et al. Severe Hypercholesterolemia, Impaired Fat Tolerance, and Advanced Atherosclerosis in Mice Lacking Both Low Density Lipoprotein Receptor-related Protein 5 and Apolipoprotein E. J. Biol. Chem. 28 March 2003, Vol. 278, No. 13, pages 11331-11336, see entire document.	1-7, 18, 19, 45
A	BOYDEN, L.M. et al. High Bone Density Due to a Mutation in LDL-Receptor-related Protein 5. New Engl. J. Med. 16 May 2002, Vol. 346, No. 20, pages 1513-1521, see entire document.	1-7, 18, 19, 45
A	VAN WESENBEECK, L. et al. Six Novel Missense Mutations in the LDL Receptor-Related Protein 5 (LRP5) Gene in Different Conditions with an Increased Bone Density. Am. J. Hum. Genet. 2003, Vol. 72, pages 763-771, see entire document.	1-7, 18, 19, 45

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

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

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INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LITTLE, R.D. et al. A Mutation in the LDL Receptor-Related Protein 5 Gene Results in the Autosomal Dominant High-Bone-Mass Trait. Am. J. Hum. Genet. 2002, Vol. 70, pages 11-19, see entire document.	1-7, 18, 19, 45
A	BABIJ, P. et al. High Bone Mass in Mice Expressing a Mutant LRP5 Gene. J. Bone Min. Res. 2003, Vol. 18, No. 6, pages 960-974, see entire document.	1-7, 18, 19, 45
A	MIZUGUCHI, T. et al. LRP5, low-density-lipoprotein-receptor-related protein 5, is a determinant for bone mineral density. J. Hum. Genet. 2004, Vol. 49, pages 80-86, see entire document.	1-7, 18, 19, 45

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/14877

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 14-17, 23 and 24
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:
Please See Continuation Sheet
3. ☒ Claim Nos.: 8-13, 20-22, 25-44 and 46-48
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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 an additional fee, this Authority did not invite payment of any additional fee.
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.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/14877

Continuation of Box I Reason 2:

Claims 14-17 recite an unlimited number of structural alterations relative to a reference structure while no functional limitations are recited. Due to the infinite number of structures encompassed by these claims, no meaningful search can be conducted. Claims 23-24 recite a large number of sequences for which no sequence identifiers have been provided. Without the sequence identifiers, no meaningful search of the sequence databases can be conducted.