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(21) International Application Number: PCT/US89/01469		150 Edgemere Road, Apt. 4, West Roxbury, MA 02132 (US). OZKAYNAK, Engin [TR/US]; 44 Purdue Drive, Milford, MA 01757 (US).	
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179,406 8 April 1988 (08.04.88) US			
232,630 15 August 1988 (15.08.88) US			
315,342 23 February 1989 (23.02.89) US			
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(63) Related by Continuation		Published	
US 179,406 (CIP)		<i>With international search report</i>	
Filed on 8 April 1988 (08.04.88)		<i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
US 232,630 (CIP)			
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(54) Title: BIOSYNTHETIC OSTEOGENIC PROTEINS AND OSTEOGENIC DEVICES CONTAINING THEM			
(57) Abstract			
Disclosed are 1) osteogenic devices comprising a matrix containing osteogenic protein and methods of inducing endochon- dral bone growth and cartilage in mammals using the devices; 2) amino acid sequence data, amino acid composition, solubility properties, structural features, homologies and various other data characterizing osteogenic proteins, 3) methods of producing osteogenic proteins using recombinant DNA technology, and 4) osteogenically and chondrogenically active synthetic protein con- structs.			


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DK	Denmark				

INTERNATIONAL SEARCH REPORT

International Application No **PCT/US 89/01469**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁴ : C 12 N 15/00, C 12 P 21/02, A 61 L 27/00, C 07 K 13/00, A 61 K 37/36, // A 61 K 35/32		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁴	C 07 K, C 12 N, C 12 P, A 61 K, A 61 L	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ¹⁰	Citation of Document, ¹¹ with Indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	WO, A, 88/00205 (GENETICS INSTITUTE) 14 January 1988 see pages 1-12, 15, 16, 17, 22-24, 49; pages 61-73, claims 1-23 cited in the application	1-6, 11, 12, 20-28, 42, 43, 46, 47
Y	--	7-10, 13- 19, 29-32, 36-41, 44, 45
Y	Cell, volume 51, 4 December 1987, Cell Press, D.L. Weeks et al.: "A maternal mRNA localized to the vegetal hemisphere in Xenopus eggs codes for a growth factor related to TGF- β ", pages 861- 867 see the whole article, especially figure 3	7-10, 13- 19, 29-32, 36-41
Y	--	7-10, 13- 19, 29-32, 36-41
Y	Nature, volume 325, 1 January 1987, R.W. Padgett et al.: "A transcript from a Drosophila pattern gene ./. .	7-10, 13- 19, 29-32, 36-41
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"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.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
8th November 1989	15. 01. 90	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	 T.K. WILLIS	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	predicts a protein homologous to the transforming growth factor- β family", pages 81-84 see figure 2 on page 82; figure 3, on page 83; figure 4 on page 84 --	
Y	The Journal of Cell Biology, volume 97, December 1983, The Rockefeller University Press, S.M. Seyedin et al.: "In vitro induction of cartilage-specific macromolecules by a bone extract", pages 1950-1953 see the whole article, especially page 1952, right-hand column --	21-41
Y	US, A, 4563350 (NATHAN et al.) 7 January 1986 see column 3, lines 30-40; column 5, lines 5-10; column 7, lines 45-60; column 10, lines 45-50 --	1, 2, 21, 22, 42, 43, 46, 47
Y	EP, A, 0128041 (BAYLINK) 12 December 1984 see pages 27-28, claims --	1, 2, 45
A	EP, A, 0169016 (COLLAGEN CORP.) 22 January 1986 see pages 19-20, claims 1-7 --	1, 2, 21, 22, 42, 43, 46, 47
A	EP, A, 0212474 (UNIVERSITY OF CALIFORNIA) 4 March 1987 --	
A	Science, volume 217, 27 August 1982, AAAS, T.H. Maugh II: "Human skeletal growth factor isolated", page 819 --	
A	S.P. Colowick et al.: "Methods in Enzymology", volume 146, "Peptide Growth Factors", part A, edited by D. Barnes et al., published by Academic Press, Inc., M. R. Urist et al.: "Preparation and bioassay of bone morphogenetic protein and polypeptide fragments", pages 294-312 --	
P,X	Science, volume 242, 16 December 1988, J.M. Wozney et al.: "Novel regulators of bone formation: molecular clones and activities", pages 1528-1534 ./..	1-6, 11, 12, 20-28, 42, 43, 46, 47

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	see the whole article cited in the application --	
L *	World Patent Information, volume 11, no. 1, 1989, Pergamon Orbit InfoLine Inc., (GB), K.E.H. Göhring et al.: "A giant step for mankind?", pages 5-10 see the whole article *(in connection with the declaration of incomplete search, see PCT/ISA/210 (Supplemental sheet 2)) --	1-47
L *	Proceedings of the Montreux 1989 International Chemical Information Conference, Montreux, CH, 26-28 September 1989, edited by Harry R. Collier, published by Infonortics Ltd, (Calne) C. Suhr: "Hypertrophic generic structures in patent claims: an extravagance and a remedy for it", pages 131-139 see the whole article *(in connection with the declaration of incomplete search, see PCT/ISA/210 (Supplemental sheet 2)) -----	1-47

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹**

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

1. Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

pls. see attached sheet

2. Claim numbers 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. Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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

1. claims 7 and 29 totally; 1 - 6, 20 - 28 and 42 - 47 partially
2. claims 8 and 30 totally; 1 - 6, 20 - 28 and 42 - 47 partially
3. claims 9, 10 and 31, 32 totally; 1 - 6, 20 - 28 and 42 - 47 partially
4. claims 11, 12 and 33, 34 totally; 1 - 6, 20 - 28 and 42 - 47 partially
5. claims 13 and 35 totally; 1 - 6, 20 - 28 and 42 - 47 partially ./.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. 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 claim numbers:
4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210 (supplemental sheet (2))

The present application is admittedly NOT the first to describe the phenomenon of bone inducing proteins, or devices containing them. It is therefore necessarily drafted to the individual compounds on well-known devices.

In claim 3, for example, a protein (on a device) is claimed, which comprises 103 amino acids, whereof 68 are completely unspecified. Even if it is assumed that "amino acid" means "natural alpha amino acid", and that "comprises" means "consisting of exactly", the formula would still cover 20⁶⁸ different compounds. The scope of the claims 1 and 2 is even vaster. (Despite this broad scope, the biological activity has only been demonstrated for the compounds COP5, COP7, COP16, and OP1, corresponding to subjects 3 and 7 of the non unity declaration!).

Formulas of the type of claim 3 cannot validly be regarded as a concise description of the matter for which protection is sought, all the more as the few defined amino acids are totally dispersed in the hypothetical peptide chain. The search has therefore been restricted to the embodiments of claims 1-47, in as far as the protein sequences correspond to the sequences disclosed in the claims 7-16 (or 29-41).

This searchable subject matter has been regrouped according to the non-unity specification, in order to establish conceptually individual subjects, each of which now constitutes a potential selection invention. (Please see also the citations "A giant step..." and "Hypertrophic Patent Claims...").

xx 6. claims 14 - 16 and 36 - 38 totally; 1 - 6, 20 - 28 and 42 - 47 partially
7. claims 17 - 19 and 39 - 41 totally; 1 - 6, 20 - 28 and 42 - 47 partially

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 8901469
SA 28080

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/12/89. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8800205	14-01-88	AU-A- 7783587	29-01-88
		EP-A- 0313578	03-05-89
US-A- 4563350	07-01-86	AU-B- 585268	15-06-89
		AU-A- 4900585	01-05-86
		EP-A- 0182483	28-05-86
		JP-A- 62016421	24-01-87
EP-A- 0128041	12-12-84	CA-A- 1229789	01-12-87
		JP-A- 60069020	19-04-85
EP-A- 0169016	22-01-86	AU-A- 4501585	23-01-86
		CA-A- 1261549	26-09-89
		JP-A- 61036223	20-02-86
		US-A- 4774322	27-09-88
		US-A- 4774228	27-09-88
		US-A- 4810691	07-03-89
		US-A- 4843063	27-06-89
EP-A- 0212474	04-03-87	US-A- 4795804	03-01-89
		JP-A- 62111933	22-05-87