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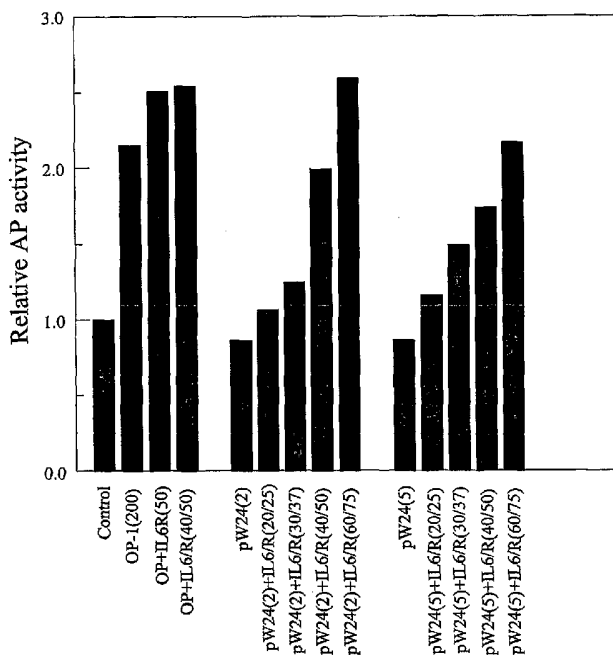
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San Antonio, Texas 78250 (US).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AE,  
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,

[Continued on next page]

(54) Title: MORPHOGENIC PROTEINS AND STIMULATORY FACTORS IN GENE THERAPY



(57) Abstract: Gene therapy methods for tissue formation, repair and regeneration using nucleic acids encoding morphogenic proteins and morphogenic protein stimulatory factors (MPSFs) are provided.

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CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG,

SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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# INTERNATIONAL SEARCH REPORT

PCT/US2005/016426

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>				
C07K14/51	A61K38/18	A61K48/00		
A61K38/25	A61K38/29	A61K38/30		
		A61K38/20		
		A61K38/19		
		A61P19/08		
According to International Patent Classification (IPC) or to both national classification and IPC				
<b>B. FIELDS SEARCHED</b>				
Minimum documentation searched (classification system followed by classification symbols)				
C07K A61K A61P				
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 practical, search terms used)				
EPO-Internal, BIOSIS, MEDLINE, WPI Data, PAJ				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>				
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 01/23563 A (STRYKER CORPORATION) 5 April 2001 (2001-04-05) page 24, line 19 - page 25, line 21; claims 1,24; figure 5; example 5 -----	1-30		
Y	US 6 048 964 A (LEE ET AL) 11 April 2000 (2000-04-11) the whole document -----	1-30		
Y	US 5 916 870 A (LEE ET AL) 29 June 1999 (1999-06-29) the whole document -----	1-30		
-/--				
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <span style="margin-left: 200px;"><input checked="" type="checkbox"/> Patent family members are listed in annex.</span>				
° Special categories of cited documents : <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> <ul style="list-style-type: none"> <li>*A* document defining the general state of the art which is not considered to be of particular relevance</li> <li>*E* earlier document but published on or after the international filing date</li> <li>*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)</li> <li>*O* document referring to an oral disclosure, use, exhibition or other means</li> <li>*P* document published prior to the international filing date but later than the priority date claimed</li> </ul> </td> <td style="width: 50%; border: none; vertical-align: top;"> <ul style="list-style-type: none"> <li>*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</li> <li>*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</li> <li>*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.</li> <li>*&amp;* document member of the same patent family</li> </ul> </td> </tr> </table>			<ul style="list-style-type: none"> <li>*A* document defining the general state of the art which is not considered to be of particular relevance</li> <li>*E* earlier document but published on or after the international filing date</li> <li>*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)</li> <li>*O* document referring to an oral disclosure, use, exhibition or other means</li> <li>*P* document published prior to the international filing date but later than the priority date claimed</li> </ul>	<ul style="list-style-type: none"> <li>*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</li> <li>*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</li> <li>*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.</li> <li>*&amp;* document member of the same patent family</li> </ul>
<ul style="list-style-type: none"> <li>*A* document defining the general state of the art which is not considered to be of particular relevance</li> <li>*E* earlier document but published on or after the international filing date</li> <li>*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)</li> <li>*O* document referring to an oral disclosure, use, exhibition or other means</li> <li>*P* document published prior to the international filing date but later than the priority date claimed</li> </ul>	<ul style="list-style-type: none"> <li>*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</li> <li>*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</li> <li>*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.</li> <li>*&amp;* document member of the same patent family</li> </ul>			
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8 September 2005		20. 12. 2005		
Name and mailing address of the ISA		Authorized officer		
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Friedrich, C		

## INTERNATIONAL SEARCH REPORT

PCT/US2005/016426

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>YEH LEE-CHUAN C ET AL: "Osteogenic protein-1 and insulin-like growth factor I synergistically stimulate rat osteoblastic cell differentiation and proliferation"            ENDOCRINOLOGY, BALTIMORE, MD, US,            vol. 138, no. 10, October 1997 (1997-10),            pages 4181-4190, XP002195402            ISSN: 0013-7227            figures 1b,2b,3; table 2</p>	1-30
Y	<p>YEH LEE-CHUAN C ET AL: "Osteogenic protein-1 and interleukin-6 with its soluble receptor synergistically stimulate rat osteoblastic cell differentiation"            JOURNAL OF CELLULAR PHYSIOLOGY,            vol. 190, no. 3, March 2002 (2002-03),            pages 322-331, XP009053501            ISSN: 0021-9541            the whole document</p>	1-30
Y	<p>KHAN S N ET AL: "Spinal fusion surgery: animal models for tissue-engineered bone constructs"            BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB,            vol. 25, no. 9, April 2004 (2004-04),            pages 1475-1485, XP004481680            ISSN: 0142-9612            table 1</p>	1-30
Y	<p>MROZ T E ET AL: "Bone graft substitutes in spinal surgery"            OPERATIVE TECHNIQUES IN ORTHOPAEDICS, SAUNDERS, PHILADELPHIA, PA, US,            vol. 13, no. 3, July 2003 (2003-07), pages 146-151, XP004677527            ISSN: 1048-6666            page 149, column 1, paragraph 3-5</p>	1-30
Y	<p>SOUTHWOOD L L ET AL: "Evaluation of Ad-BMP-2 for enhancing fracture healing in an infected defect fracture rabbit model"            JOURNAL OF ORTHOPAEDIC RESEARCH, THE JOURNAL OF BONE AND JOINT SURGERY, INC.,, US,            vol. 22, no. 1, January 2004 (2004-01),            pages 66-72, XP004722552            ISSN: 0736-0266            the whole document</p>	1-30

# INTERNATIONAL SEARCH REPORT

PCT/US2005/016426

## Box 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:  
  
Although claims 1-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box 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:

see additional 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 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.:  
  
1-30 (in part)

### Remark on Protest

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

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

## 1. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with OP-1 and a MPSF  
---

## 2. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with OP-2 and a MPSF  
---

## 3. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with OP-3 and a MPSF  
---

## 4. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with COP-1 and a MPSF  
---

## 5. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with COP-3 and a MPSF  
---

## 6. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with COP-4 and a MPSF  
---

## 7. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with COP-5 and a MPSF  
---

## 8. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with COP-7 and a MPSF  
---

## 9. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with COP-16 and a MPSF

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-2 and a MPSF

11. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-3 and a MPSF

12. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-3b and a MPSF

13. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-4 and a MPSF

14. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-5 and a MPSF

15. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-6 and a MPSF

16. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-9 and a MPSF

17. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-10 and a MPSF

18. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-11 and a MPSF

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with CDMP-3 and a MPSF

---

20. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-12 and a MPSF

---

21. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with CDMP-2 and a MPSF

---

22. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-13 and a MPSF

---

23. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with CDMP-1 and a MPSF

---

24. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-14 and a MPSF

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25. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-15 and a MPSF

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26. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-16 and a MPSF

---

27. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-17 and a MPSF

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## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

28. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with BMP-18 and a MPSF

---

29. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-1 and a MPSF

---

30. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-2 and a MPSF

---

31. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-3 and a MPSF

---

32. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-5 and a MPSF

---

33. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-6 and a MPSF

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34. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-7 and a MPSF

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35. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-8 and a MPSF

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36. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-10 and a MPSF

---

37. claims: 1-30 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Induction of differentiation or proliferation in progenitor cells with GDF-11 and a MPSF  
---

38. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-12 and a MPSF  
---

39. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with MP121 and a MPSF  
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40. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with dorsalin-1 and a MPSF  
---

41. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with DPP and a MPSF  
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42. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with Vg-1 and a MPSF  
---

43. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with Vgr-1 and a MPSF  
---

44. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with 60A protein and a MPSF  
---

45. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with NODAL and a MPSF  
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46. claims: 1-30 in part

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Induction of differentiation or proliferation in progenitor cells with UNIVIN and a MPSF  
---

47. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with SCREW and a MPSF  
---

48. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with ADMP and a MPSF  
---

49. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with NEURAL and a MPSF  
---

50. claims: 1-30 in part

Induction of differentiation or proliferation in progenitor cells with GDF-9 and a MPSF  
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## INTERNATIONAL SEARCH REPORT

PCT/US2005/016426

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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US 5916870	A	29-06-1999	NONE	
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