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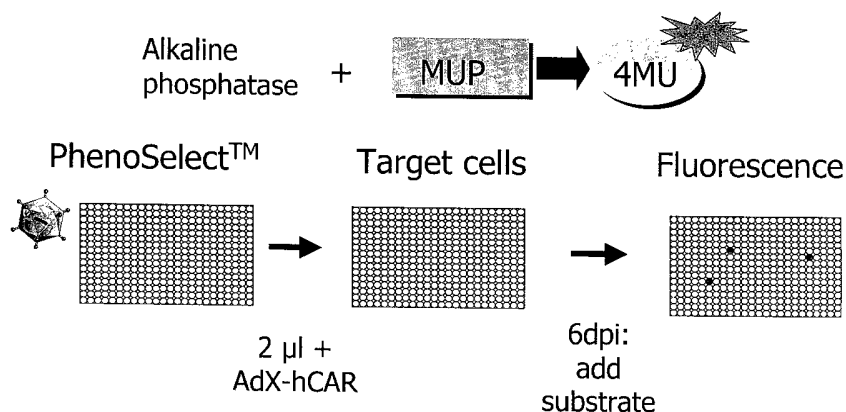
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[Continued on next page]

(54) Title: MODULATORS OF BONE HOMEOSTASIS IDENTIFIED IN A HIGH-THROUGHPUT SCREEN

## Fluorescent detection of AP



(57) Abstract: The invention relates to the field of molecular genetics and medicine. In particular, the present invention relates to the field of functional genomics, i.e., to a method for the identification of genes that function in regulating bone homeostasis, such as the induction of osteogenesis. In particular, the present invention relates to polynucleotides and the encoded polypeptides that are identified in a high-throughput screen designed to detect modulation of bone alkaline phosphatase activity. Moreover, the present invention relates to vectors, host cells, antibodies and diagnostic methods for detecting diseases involving the discovered polynucleotides, and therapeutic methods for treating such diseases. The invention further relates to methods and means for drug compound screens designed to develop new therapeutic strategies.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/09530

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/10 C12N15/12 C07K14/51 A61K48/00 C07K16/18  
 A61K39/395 C12Q1/68 A61K38/17 A01K67/027 G01N33/68  
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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 7 C12N C07K A61K C12Q G01N

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)

SEQUENCE SEARCH, EMBL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                               | Relevant to claim No.          |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| X          | WO 00 06726 A (AMGEN INC. (US); SHUTTER JOHN R.; STARK KEVIN L.)<br>10 February 2000 (2000-02-10)                                                                                                                                                | 1-4,6-8,<br>11-18,<br>29-31,37 |
| Y          | the whole document                                                                                                                                                                                                                               | 5                              |
| Y          | ---<br>WO 99 64582 A (INTROGENE B.V. (NL); SCHOUTEN G.; VOGELS R.; BOUT A.; VAN ES H.) 16 December 1999 (1999-12-16)<br>cited in the application<br>page 27 -page 28                                                                             | 5                              |
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|            | -/--                                                                                                                                                                                                                                             |                                |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in 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 document but published on or after the international filing date

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"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

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/09530

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                | Relevant to claim No.          |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| X          | EP 1 004 669 A (ASAHI KASEI KOGYO KABUSHIKI KAISHA OSAKA-SHI, OSAKA (JP); SAKANO SEIJI) 31 May 2000 (2000-05-31)<br>the whole document<br>---                                                                                                                                                                                                     | 1-4,6-8,<br>11-18,<br>29-31,37 |
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| A          | DALLAS D.J. ET AL: "Stimulation of osteoblast differentiation and bone formation in vitro and in vivo by Notch receptor-ligand interactions"<br>JOURNAL OF BONE AND MINERAL RESEARCH, vol. 14, no. SUPPL 1, September 1999 (1999-09), page S172<br>XP002237112<br>ISSN: 0884-0431<br>Abstract 1157<br>the whole document<br>---                   |                                |
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| A          | LOU J. ET AL.: "Gene therapy: adenovirus-mediated human bone morphogenetic protein-2 gene transfer induces mesenchymal progenitor cell proliferation and differentiation in vitro and bone formation in vivo"<br>JOURNAL OF ORTHOPAEDIC RESEARCH, vol. 17, no. 1, January 1999 (1999-01), pages 43-50, XP002194122<br>the whole document<br>----- |                                |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 02/09530

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 9  
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:  
see FURTHER INFORMATION sheet PCT/ISA/210
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 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:

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.:  
1-41 all partially, insofar as they refer to subject-matter related to inventions 1 and 3 (Nucleic acid as in SEQ ID NO:1, 3, 7; polypeptide as in SEQ ID NO:2, 4, 8; related products, uses, methods, compositions thereof).
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.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 21, 22 and 39 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.

Although claim 26 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

## Continuation of Box I.2

Claims Nos.: 9

Present claim 9 relates to a method for regulating gene expression of a target gene, without giving any true technical characterization of said target gene.

Moreover, no specific target genes are defined in present application (see page 34).

In consequence, the scope of said claim is ambiguous and vague and its subject-matter is not sufficiently disclosed and supported (Articles 5 and 6 PCT).

No search can be carried out for such purely speculative claim whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 1-41 all in part

Nucleic acid consisting of a sequence as in SEQ ID NO:1, SEQ ID NO:3, encoding a polypeptide as in SEQ ID NO:2, SEQ ID NO:4. Polypeptide encoded by said nucleic acid.  
Related products, uses, methods, compositions thereof.

2. Claims: 1-41 all in part

Nucleic acid consisting of a sequence as in SEQ ID NO:5, encoding a polypeptide as in SEQ ID NO:6.  
Polypeptide encoded by said nucleic acid.  
Related products, uses, methods, compositions thereof.

3. Claims: 1-41 all in part

Nucleic acid consisting of a sequence as in SEQ ID NO:7, encoding a polypeptide as in SEQ ID NO:8.  
Polypeptide encoded by said nucleic acid.  
Related products, uses, methods, compositions thereof.

4. Claims: 1-41 all in part

Nucleic acid consisting of a sequence as in SEQ ID NO:9, encoding a polypeptide as in SEQ ID NO:10.  
Polypeptide encoded by said nucleic acid.  
Related products, uses, methods, compositions thereof.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/09530

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s)                                                                                                                                                                                                           | Publication<br>date                                                                                                                                                                |
|-------------------------------------------|---|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| WO 0006726                                | A | 10-02-2000          | AU 4870599 A<br>CA 2337492 A1<br>EP 1100899 A2<br>JP 2002523018 T<br>WO 0006726 A2                                                                                                                                                   | 21-02-2000<br>10-02-2000<br>23-05-2001<br>30-07-2002<br>10-02-2000                                                                                                                 |
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