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— *of inventorship (Rule 4.17(iv))*

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10 April 2008

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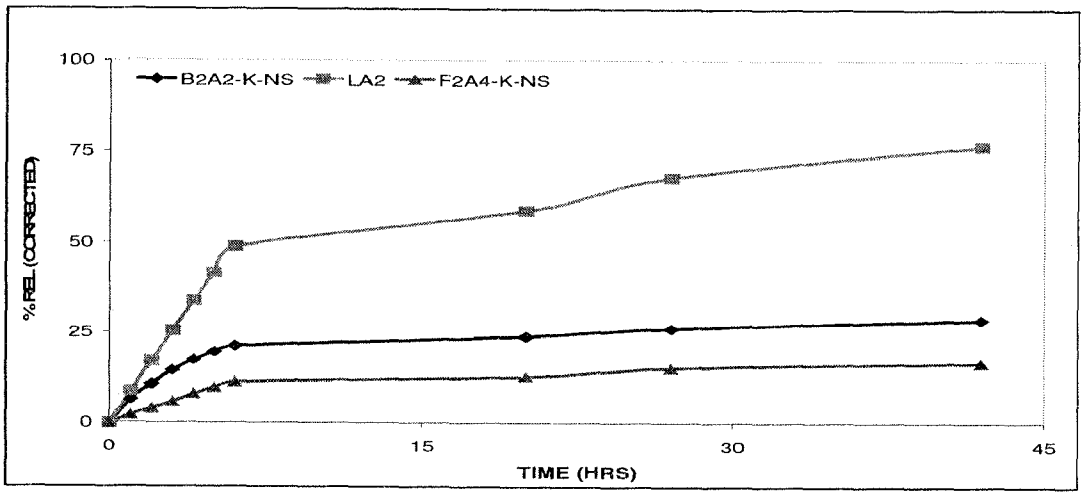
15 May 2008

(54) Title: COMPOSITION AND METHOD FOR DELIVERY OF BMP-2 AMPLIFIER/CO-ACTIVATOR FOR ENHANCEMENT OF OSTEOGENESIS



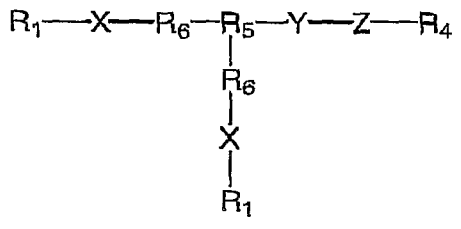
(57) Abstract: A composition comprising a synthetic growth factor analogue comprising a non-growth factor heparin binding region, a linker and a sequence that binds specifically to a cell surface receptor and an osteoconductive material where the synthetic growth factor analogue is attached to and can be released from the osteoconductive material and is an amplifier/co-activator of osteoinduction.

WO 2007/150053 A3

AMENDED CLAIMS
received by the International Bureau on 06 February 2008

WHAT IS CLAIMED IS:

1. A compound of formula II:



wherein:

the compound of formula II modulates the response to bone morphogenetic proteins;

X is a peptide chain that (i) has a minimum of three amino acid residues, (ii) has a maximum of about fifty amino acid residues, and (iii) binds specifically to a cell surface receptor;

R_1 is independently hydrogen, such that the terminal group is NH_2, an acyl group with a linear or branched C_1 to C_{17} alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl chain including an N-terminus NH_2, NH_3^+, or NH group or a corresponding acylated derivative, or is amino acid, a dipeptide or a tripeptide with an N-terminus NH_2, NH_3^+, or NH group;

R_6 is independently a linker comprising a chain from 0 to about 15 backbone atoms covalently bonded to R_3 when the linker is greater than 0 atoms;

R_5 is a trifunctional alpha amino acid residue, wherein X is covalently bonded through a side chain of R_3;

R_4 is OH such that the terminal group is a carboxyl, NH_2, an acyl group with a linear or branched C_1 to C_{17} alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl

chain including an N-terminus NH_2, NH_3^+, or NH group or a corresponding acylated derivative, or NH-R_1;

Y is a linker comprising a chain from 0 to about 50 backbone atoms covalently bonded to R_5 and Z; and

Z is a non-signaling peptide chain that includes a heparin binding domain comprising an amino acid sequence that comprises (i) a minimum of one heparin binding motif, (ii) a maximum of about ten heparin binding motifs, and (iii) a maximum of about thirty amino acids.

2. A composition comprising:

a synthetic growth factor analogue of claim 1; and

an osteoconductive material comprising one or more of an inorganic material, a synthetic polymer, a natural polymer, an allograft bone, or combination thereof,

wherein the synthetic growth factor analogue is attached to and can be released from the osteoconductive material and is an amplifier/co-activator of osteoinduction.

3. The compound of claim 2 wherein the osteoconductive material is formed into a granule, a putty, a powder, a gel, a block or a combination thereof.

4. The composition of claim 2 wherein the growth factor analogue is AISMLYLDENEKVVLKK(AISMLYLDENEKVVLK)HxHxHxRKRLDRIARNH$_2$

6. The composition of claim 2 wherein the growth factor analogue modulates the osteloinductive environment by amplifying or co-activating cell growth, chemotaxis, or cell attachment.

7. The composition of claim 2, further comprising a calcium sulfate salt as the osteoconductive material.

8. The composition of claim 7 wherein the calcium sulfate is between about 30-80 wt %.

9. The composition of claim 2 wherein the osteoconductive material contains about 0-100 wt % hydroxyapatite and about 0-100 wt % tricalcium phosphate.

10. The composition of claim 2 wherein the osteoconductive material contains about 20 wt % hydroxyapatite and about 80 wt % tricalcium phosphate.

11. The composition of claim 2 wherein the osteoconductive material is selected from hydroxyapaptite, tricalcium phosphate, collagen, hyaluronate, calcium sulfate, polyglycolic acid fibers, polylactic-co-glycolic acid, allograft or any combination thereof.

12. The composition of claim 2 in which the formulation contains excipients which do not interfere with peptide binding to the osteoconductive matrix.

13. The composition of claim 2 wherein the granule further comprises silicate substituting a portion of the phosphate ions in the hydroxyapatite lattice.

14. A method for treating bone lesions comprising:

coating an osteoconductive material of claim 2 with the synthetic growth factor analogue of claim 1 to generate an osteoconductive material with the growth factor analogue releasably attached thereto; and

implanting the coated osteoconductive material in a bone lesion.

15. The method of claim 14 in which an exogenous or recombinant bone growth factor is added.

16. The method of claim 14 wherein the osteoconductive material comprises one or more inorganic material, collagen, hyaluronate, Polylactic acid, Polyglycolic acid, allograft or any combination thereof.

17. The method of claim 14 wherein the osteoconductive material are formed from granules, polymers, powders, gel, cement, putty or any combination thereof.

18. The method of claim 14 wherein the osteoconductive material is used in combination with a load bearing device to treat bone lesions.

19. The method of claim 18 wherein the load bearing device is selected from cages, wedges, rods, pedicle screws, vertebral body replacement, intervertebral body fusion device or rings for bone fusion.

20. The method of claim 18 wherein the treatment of the bone lesion results in spine fusion.

21. The method of claim 14 wherein the method further comprises adding host bone chips or bone marrow aspirate with the graft material.

22. The method of claim 14 wherein the synthetic growth factor analogue comprises AISMLYLDENEKVVLKK(AISMLYLDENEKVVLK)HxHxHxRKRLDRIARNH$_2$.

23. The method of claim 14 wherein releasing the synthetic growth factor analogue is rate-controlled by manipulating the composition of the osteoconductive material, concentration of synthetic growth factor analogue attached to the osteoconductive material or the physical properties of the osteoconductive material.

24. A kit comprising:

a lyophilized vial of synthetic growth factor analogue (with or without excipients); and a container of osteoconductive material.

AMENDMENT AND STATEMENT UNDER ARTICLE 19

International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20
SWITZERLAND

Dear Sir:

In response to the Examiner's comments in the International Search Report mailed on 06 December 2007, Applicant respectfully submits the attached replacement sheets 39-43 of the PCT Request as originally filed.

This application was submitted with 24 claims. The following Article 19 amendments were made to the claims in response to receiving the International Search Report:

Claims 15-21 and 23 remain unchanged.

Claims 1-14 and 22 have been replaced by amended claims bearing the same number.

Claim 5 has been deleted.

The amendments were made in response to the Examiner's comments. Substitute sheets are attached.

No new matter is believed to be introduced by the amended claims.

Respectfully submitted,

Date: 2/6/08

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