

CLAIMS

1. A multi-part composition for 3-dimensional printing of a bone composite, the multi-part composition comprising:
 - 5 i) a first part comprising fibrinogen in a pharmaceutically acceptable carrier;
 - ii) a second part comprising thrombin in a pharmaceutically acceptable carrier;
 - and
 - iii) a third part comprising a pharmaceutically acceptable hydrogel mixed with at least one biocompatible inorganic material, the at least one biocompatible inorganic material providing a source of at least one of calcium and phosphorous atoms,
 - 10 wherein the third part has an apparent viscosity selected from the group consisting of:
 - from about 1 to about 300 Pa·s at a shear rate of 0.1 s^{-1} as measured by a rotational viscometer at 25 °C and 1 atm of pressure, and
 - 15 from about 1 to about 100 Pa·s at a shear rate of 1 s^{-1} as measured by a rotational viscometer at 25 °C and 1 atm of pressure,
 - and further wherein the third part is a standalone composition, or it is mixed with either the first part or the second part of the multipart composition, such that at least the first and second parts of the
 - 20 multi-part composition do not mix prior to printing by a 3-dimensional printing device.
2. A composition according to claim 1, wherein in said first part the fibrinogen is at a concentration between about 5 to about 200 mg/mL.
- 25 3. A composition according to any of the preceding claims, wherein in said second part the thrombin is at a concentration about 25 and about 1500 IU/mL.
4. A composition according to any of the preceding claims, wherein the third part of the multipart composition has an apparent viscosity selected from the group consisting of:
 - 30 from about 50 to about 250 Pa·s at a shear rate of 0.1 s^{-1} as measured by rotational viscometer at room temperature and pressure, and
 - from about 2 to about 50 Pa·s at a shear rate of 1 s^{-1} as measured by rotational viscometer at room temperature and pressure.
- 35 5. A composition according to any of the preceding claims, wherein said third part is a standalone composition such that the three parts of the multipart composition do not mix prior to printing by a 3-dimensional printing device.
- 40 6. A composition according to any of the preceding claims, wherein said biocompatible inorganic material is selected from the group consisting of bioglass, tricalcium phosphate, single-phase hydroxyapatite, biphasic hydroxyapatite-tricalcium phosphate, natural bone powder, and combinations thereof.

7. A composition according to any of the preceding claims, wherein said biocompatible inorganic material is selected from the group consisting of tricalcium phosphate, single-phase hydroxyapatite, biphasic hydroxyapatite-tricalcium phosphate, and combinations thereof.
- 5 8. A composition according to any of the preceding claims, wherein the biocompatible inorganic material is beta-tricalcium phosphate.
9. A composition according to claim 8 wherein the beta-tricalcium phosphate has a density of between about 2.95 g/cm³ and about 3.15 g/cm³ as determined by helium pycnometry.
- 10 10. A composition according to claim 8 wherein the beta-tricalcium phosphate has a density of between about 2.95 g/cm³ and about 3.10 g/cm³ as determined by helium pycnometry.
11. A composition according to anyone of claims 8 to 10 wherein the beta-tricalcium phosphate has a
15 d90 particle size distribution of not more than about 180 µm.
12. A composition according to anyone of claims 8 to 11 wherein the beta-tricalcium phosphate has a d90 particle size distribution of not more than about 160 µm.
- 20 13. A composition according to anyone of claims 8 to 12 wherein the beta-tricalcium phosphate is characterized by an X-ray powder diffraction pattern comprising unique peaks at 2θ (d value Å); angles of 17.0 (5.2), 21.9 (4.1), 25.8 (3.45), 27.8 (3.2), 29.65 (3.0), 31.0 (2.9), 32.45 (2.75), 34.4 (2.6), 46.9 (1.9), 48.0 (1.9), 48.4 (1.9), and 53.0 (1.7) when obtained with a Cu tube anode with K-alpha radiation.
- 25 14. A composition according to any of the preceding claims, wherein said biocompatible inorganic material has an average particle size of less than about 150 µm.
15. A composition according to any of the preceding claims, wherein said biocompatible inorganic
30 material has an average particle size of less than about 100 µm.
16. A composition according to any of the preceding claims, wherein the biocompatible inorganic material is hydrated with an albumin solution prior to mixing with the pharmaceutically acceptable hydrogel.
- 35 17. A composition according to any of the preceding claims, wherein the pharmaceutically acceptable hydrogel is selected from the group consisting of a hydrogel comprised of a hydrophilic polysaccharide, gelatin, and combinations thereof.
- 40 18. A composition according to any of the preceding claims, wherein said pharmaceutically acceptable hydrogel is selected from the group consisting of alginate, hyaluronic acid, gelatin and combinations thereof.
- 45 19. A composition according to any of the preceding claims, wherein said pharmaceutically acceptable hydrogel comprises an alginate.

20. A composition according to any of the preceding claims, wherein said third part has a ratio of biocompatible inorganic material:hydrogel of between about 1 - 10 g of biocompatible inorganic material to about 1 mL of hydrogel.
- 5 21. A composition according to any of the preceding claims, wherein said composition further comprises a material with osteoconductive, osteoinductive, and/or osteogenic properties.
22. A composition according to claim 21 wherein the material with osteoconductive, osteoinductive, and/or osteogenic properties is selected from the group consisting of cells, proteins, growth
10 factors, and combinations thereof.
23. A composition according to any of the preceding claims, wherein said composition further comprises human mesenchymal stem cells (hMSC).
- 15 24. A composition according to claim 23, wherein said hMSC are at a concentration between 1×10^3 to about 5×10^{10} hMSC per mL of pharmaceutically acceptable hydrogel.
25. A bone composite obtainable from the multi-part composition according to any of claims 1 to 24.
- 20 26. A bone composite according to claim 25, wherein said biocompatible inorganic material is at a concentration of between about 5% w/w to about 60% w/w of the bone composite.
27. A method for preparing a bone composite, the method comprising the steps of:
- 25 i) providing a 3-dimensional printing device with the multi-part composition of any one of claims 1-24;
- ii) printing the bone composite according to a determined design; and
- iii) optionally incubating the bone composite.
28. The method of claim 27, wherein the 3-dimensional printing device prints,
- 30 i) a first layer comprising either fibrinogen or thrombin;
- ii) a second layer comprising either fibrinogen or thrombin;
- wherein if the first layer comprises fibrinogen the second layer comprises thrombin and *vice versa*,
- 35 iii) sequentially repeating steps i) and ii) n times, wherein $n \geq 1$, to generate an alternating layered structure;
- iv) printing the third part comprising the hydrogel and biocompatible inorganic material on top of the alternating layered structure of step iii); and
- v) optionally repeating steps i) - iv) as necessary to provide the bone composite.
- 40 29. The method of claim 28, wherein the fibrinogen is printed first, and the thrombin is printed second as a layer on top of the fibrinogen.
30. The method of any one of claims 28 to 29, wherein,
- 45 i) the first layer has a defined volume of X,
- ii) the second layer has a defined volume of Y,

- iii) steps i) and ii) are repeated n times, wherein $n \geq 1$, to generate an alternating layered structure of volume $nX + nY$; and
- iv) the third part comprising the hydrogel and biocompatible inorganic material is printed on top of the alternating layered structure of step iii), the third part having a volume Z .
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31. The method of claim 30, wherein the volumes X and Y are the same such that the volume $nX = nY$.
32. The method of any one of claims 30 or 31, wherein the ratio of Z to nX to nY ($Z:nX:nY$) is about 0.60-1.0 : 1 : 1.
- 10 33. The method of any one of claims 29 to 32 wherein $2 \leq n \leq 10$.
34. The method of claim 27 wherein the 3-dimensional printing device prints;
- 15 i) a first layer comprising the third part of the multipart composition of the present invention;
- ii) a second layer comprising either fibrinogen or thrombin;
- iii) a third layer comprising either fibrinogen or thrombin;
- wherein if the second layer comprises fibrinogen the third layer comprises thrombin *and vice versa*, and
- 20 iv) sequentially repeating steps ii) and iii) n times, wherein $n \geq 1$, to generate an alternating layered structure of fibrinogen and thrombin; and
- v) optionally repeating steps i) - iv) as necessary to provide the bone composite
- 25 35. The method of claim 34 wherein,
- i) the first layer has a defined volume of A ,
- ii) the second layer has a defined volume of B ,
- iii) the third layer has a defined volume of C ,
- 30 iv) wherein steps ii) and iii) may be repeated n times, wherein $n \geq 1$, to generate a layered structure of volume $A + nB + nC$.
36. The method of claim 35 wherein the ratio of A to nB to nC ($A:nB:nC$) is about 1 - 5 : 1 : 1.
- 35 37. The method of claim of any one of claims 34 to 36 wherein $2 \leq n \leq 10$.
38. The method of claim 27, wherein the composition of claims 1 to 24 is a two-part composition and the method comprises the steps of:
- 40 i) printing the first part of the composition comprising either fibrinogen or thrombin;
- ii) repeating step i) n times, wherein $n \geq 1$, to generate a layered structure comprising only one of fibrinogen or thrombin;
- iii) printing the second part comprising the other of fibrinogen or thrombin mixed with the pharmaceutically acceptable hydrogel and the biocompatible inorganic material on top of the layered structure generated in step ii);

- iv) optionally repeating steps i) - iii) as necessary to provide the bone composite
39. The method of claim 27, wherein the composition of claims 1 to 24 is a two-part composition and the method comprises the steps of:
- 5 i) printing the second part comprising one of fibrinogen or thrombin mixed with the pharmaceutically acceptable hydrogel and the biocompatible inorganic material;
- ii) printing the first part comprising the other of fibrinogen or thrombin on top of the part printed in step i);
- iii) repeating step ii) n times, wherein $n \geq 1$, to generate a layered structure
- 10 iv) optionally repeating steps i) - iii) as necessary to provide the bone composite.
40. A bone composite obtainable from the method of any one of claims 27 to 39.
41. A method of treating a bone injury, or bone defect in a patient in need thereof comprising the step
- 15 of implanting the bone composite of claims 25 to 26, or 40 into the patient in need thereof.
42. Use of the synthetic bone composite according to claims 25 to 26, or 40 in the treatment of a bone injury, or a bone defect.
- 20 43. A kit comprising a 3-dimensional printer and the multi-part composition according to anyone of claims 1 to 24.