US009427469B2

(12) **United States Patent**
**Ouyang et al.**

(10) **Patent No.: US 9,427,469 B2**
(45) **Date of Patent: Aug. 30, 2016**

(54) **SOLUBLE PHYSIOLOGICAL CHITOSAN FORMULATIONS COMBINED WITH PLATELET-RICH PLASMA (PRP) FOR TISSUE REPAIR**

(75) Inventors: **Wei Ouyang**, Montreal (CA); **Michael Buschmann**, Montreal (CA); **Anik Chevrier**, Pointe-Claire (CA)

(73) Assignee: **ORTHO REGENERATIVE TECHNOLOGIES INC.**, Quebec (CA)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/510,663**

(22) PCT Filed: **Nov. 19, 2010**

(86) PCT No.: **PCT/CA2010/001858**

§ 371 (c)(1),
(2), (4) Date: **Sep. 4, 2012**

(87) PCT Pub. No.: **WO2011/060555**

PCT Pub. Date: **May 26, 2011**

(65) **Prior Publication Data**

US 2013/0004474 A1 Jan. 3, 2013

**Related U.S. Application Data**

(60) Provisional application No. 61/262,792, filed on Nov. 19, 2009.

(51) **Int. Cl.**

| | |
|---|---|
| ***A01N 63/00*** | (2006.01) |
| ***A01N 65/00*** | (2009.01) |
| ***A61K 45/06*** | (2006.01) |
| ***A61K 31/722*** | (2006.01) |
| ***A61K 33/14*** | (2006.01) |
| ***A61K 35/16*** | (2015.01) |
| ***A61L 27/20*** | (2006.01) |
| ***A61L 27/36*** | (2006.01) |
| ***C08L 5/08*** | (2006.01) |
| *C08K 3/16* | (2006.01) |
| *C08K 5/521* | (2006.01) |

(52) **U.S. Cl.**

CPC ..... ***A61K 45/06*** (2013.01); ***A61K 31/722*** (2013.01); ***A61K 33/14*** (2013.01); ***A61K 35/16*** (2013.01); ***A61L 27/20*** (2013.01); ***A61L 27/3616*** (2013.01); ***C08L 5/08*** (2013.01); *C08K 3/16* (2013.01); *C08K 5/521* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

| | | | | |
|---|---|---|---|---|
| 5,510,102 | A * | 4/1996 | Cochrum | 424/78.08 |
| 5,614,204 | A * | 3/1997 | Cochrum | 424/423 |
| 5,885,609 | A * | 3/1999 | Amiji | 424/425 |
| 6,322,785 | B1 * | 11/2001 | Landesberg et al. | 424/93.72 |
| 6,624,245 | B2 * | 9/2003 | Wallace et al. | 525/54.1 |
| 2002/0165337 | A1 * | 11/2002 | Wallace et al. | 528/373 |
| 2002/0197302 | A1 * | 12/2002 | Cochrum et al. | 424/445 |
| 2003/0007957 | A1 * | 1/2003 | Britton et al. | 424/93.72 |
| 2003/0152639 | A1 * | 8/2003 | Britton et al. | 424/529 |
| 2004/0078077 | A1 * | 4/2004 | Binette et al. | 623/13.17 |
| 2004/0078090 | A1 * | 4/2004 | Binette et al. | 623/23.76 |
| 2004/0208845 | A1 * | 10/2004 | Michal et al. | 424/78.24 |
| 2005/0125077 | A1 * | 6/2005 | Harmon et al. | 623/23.72 |
| 2005/0226916 | A1 * | 10/2005 | Cochrum et al. | 424/445 |
| 2007/0053957 | A1 * | 3/2007 | Kennedy et al. | 424/443 |
| 2009/0148486 | A1 * | 6/2009 | Lu et al. | 424/422 |
| 2013/0004474 | A1 * | 1/2013 | Ouyang et al. | 424/93.72 |

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| WO | WO 96/23039 | 8/1996 |
| WO | WO 99/07416 | 2/1999 |
| WO | WO 2006/015178 | 2/2006 |
| WO | WO2008/064487 | 6/2008 |

OTHER PUBLICATIONS

Rinaudo et al (Polymer, 40:7029-7032 (1999).*

Hoemann et al., The Journal of Bone and Joint Surgery, 87:2671-2686 (2005). "Chitosan-glycerol phosphate/blood implants improve hyaline cartilage repair in ovine microfracture defects."

Akeda, K. et al., Osteoarthritis and Cartilage,14:1272-1280 (2006). "Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis."

Casati, M.Z. et al., Int. J. Oral Maxillofac. Surg., 36:132-136 (2007). "Platelet-rich plasma does not improve bone regeneration around peri-implant bone defects—a pilot study in dogs."

Chenite, A. et al., Biomater., 21:2155-2161 (2000). "Novel injectable neutral solutions of chitosan form biodegradable gels in situ."

Chenite, A. et al., Carbohyd. Polym., 46:39-47 (2001). "Rheological characterization of thermogelling chitosan/glycerol-phosphate solutions."

Luengo Gimeno, F. et al., Thrombosis Journal, 4:18¬ 25 (2006). "Preparation of platelet-rich plasma as a tissue adhesive for experimental transplantation in rabbits."

Hoemann, C.D. et al., Osteoarthritis & Cartilage,15:78-89 (2007). "Chitosan-glycerol phosphate/blood implants elicit hyaline cartilage repair integrated with porous subchondral bone in microdrilled rabbit defects."

Mendonca-Caridad, J.J. et al., Int. J. Oral Maxillofac. Surg., 35:88-91 (2006). "Frontal sinus obliteration and craniofacial reconstruction with platelet rich plasma in a patient with fibrous dysplasia."

Ranly, D.M. et al., J. Bone Joint Surg. Am., 89:139-147 (2007). "Platelet-rich plasma inhibits demineralized bone matrix-induced bone formation in nude mice."

(Continued)

*Primary Examiner* — Thomas J Visone

(74) *Attorney, Agent, or Firm* — Eric L. Lane; Green Patent Law

(57) **ABSTRACT**

The present disclosure relates to an activated polymer composition for use in repairing tissue of a patient comprising platelet-rich plasma (PRP), a chitosan solution, a salt such as NaCl or glycerol phosphate, and an activator such as at least one of $CaCl_2$ and a mixture of thrombin/$CaCl_2$.

**16 Claims, 11 Drawing Sheets**