reduces the overall net bone formation. Moreover, porous biomaterials are used for overall bone regeneration by delivering rhBMP-2, but Horstmann and co-workers have reported that these materials tend to protrude into the cortical bone and delay cortical healing (Horstmann *et al*. (2018), Tissue Eng. Part A, Vol. 23). Thus, from a clinical perspective there is a need to have a membrane in the form of a thin biomaterial that can prevent cancellous bone void fillers from protruding into the cortical bone and simultaneously promote the natural course of cortical bone healing by providing a template for cells and local release of growth factors. The process of cancellous bone healing is different than cortical bone healing and this invention is primarily intended for cortical bone regeneration. The cancellous bone can be treated with any bone substitute but the cortical bone requires specific biomaterial properties.

Thus, there remains a need for improved bone repair methods especially the development of an artificial periosteum which could also be used to deliver bone active agents like BMP-2 locally over extended periods of time to promote bone growth and repair bone defects.

SUMMARY

The present invention provides an artificial periosteum and methods related to bone repair and local delivery of therapeutic agents into a bone. The therapeutic agents may be bone active agents which repair bone defects and otherwise promote bone growth, bone active agents that treat bone-related pain, anti-inflammatory agents to treat inflammation-related conditions (e.g., arthritis), anti-cancer drugs to treat bone cancer, or antimicrobial agents to treat or prevent infection at the treatment site or combinations thereof.

One aspect of the invention provides an artificial periosteum comprising a functionalized collagen-containing membrane and a drug-carrier mixture, wherein the drug-carrier mixture comprises at least one therapeutic agent and a calcium-containing carrier mixture.

Another aspect of the invention provides a method of repairing bone, comprising the step of implanting an artificial periosteum comprising a functionalized collagen-containing membrane and a drug-carrier mixture, wherein the drug-carrier mixture comprises at least one therapeutic agent and a calcium-containing carrier mixture.

Also disclosed is an artificial periosteum comprising a functionalized collagen-containing membrane and a drug-carrier mixture for use in a method of repairing bone, wherein the

drug-carrier mixture comprises at least one therapeutic agent and a calcium-containing carrier mixture.

In certain embodiments of the invention, the functionalized collagen-containing membrane is a hydroxyapatite functionalized collagen-containing membrane, while the calcium-containing carrier mixture is collagen based.

Thus, in one aspect the present invention provides an artificial periosteum comprising a hydroxyapatite functionalized collagen-containing membrane and a drug-carrier mixture, wherein the drug-carrier mixture comprises BMP-2 and zoledronic acid (ZA).

In certain embodiments of the invention, the therapeutic agent is a bone active agent which comprises a compound that activates osteoblasts. In other embodiments, the therapeutic agent is a bone active agent that inhibits osteoclasts. In still other embodiments, the therapeutic agent is a bone active agent which comprises one or more of: PGE1; PGE2; an EP2 receptor agonist; an EP4 receptor agonist; an EP2 receptor/EP4 receptor dual agonist; an organic bisphosphonate; a cathepsin K inhibitor; an estrogen or an estrogen receptor modulator; calcitonin; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; a RANKL inhibitor; a bone anabolic agent; a bone morphogenetic agent; Vitamin D or a synthetic Vitamin D analogue; an androgen or an androgen receptor modulator; a SOST inhibitor; platelet-derived growth factor; a pharmaceutically acceptable salt thereof; and a mixture thereof.

One aspect of the invention provides a method of repairing bone, comprising the step of implanting an artificial periosteum comprising a functionalized collagen-containing membrane and a drug-carrier mixture, wherein the drug-carrier mixture comprises BMP-2 and zoledronic acid.

In one embodiment, the functionalized collagen-containing membrane is a hydroxyapatite functionalized collagen-containing membrane.

Also disclosed is an artificial periosteum comprising a functionalized collagen-containing membrane and a drug-carrier mixture for use in a method of repairing bone in a patient, wherein the drug-carrier mixture comprises BMP-2 and zoledronic acid

In one aspect of the invention provides a method of repairing a bone defect in a patient, wherein the method comprises the step of:

(i) implanting into said bone defect a bone graft material; and

(ii) covering said graft with a hydroxyapatite functionalized collagen-containing membrane.

Also disclosed is a bone graft material covered with a hydroxyapatite functionalized collagen-containing membrane for use in a method of repairing a bone defect in a patient.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows an overview of the material structure and collagen fiber alignment.

Figure 2 shows a surgical procedure of the tibia defect model.

Figure 3 shows micro-CT quantifications of the tibia defect study 8-weeks post-surgery.

Figure 4 shows the evaluation of cortical healing using micro-CT.

Figure 5 shows the histological analysis of tibia defect healing.

Figure 6 shows X-Ray radiography of specimens harvested from the abdominal muscle pouch 4 weeks post-surgery.

Figure 7 shows the role of collagen membrane as a containment device for ceramic or polymeric biomaterials placed within a bone void.

Figure 8 shows a comparative study of an absorbable collagen sponge (ACS) produced by Medtronic, which is sold as INFUSE® bone graft, together with solution containing rhBMP-2, with the collagen-containing membrane of the present invention comprising rhBMP-2 and ZA. Data are CT data and represent average ± SD (shown at top), n=8/group for ACS and n=5/group for collagen membrane.

CLAIMS

1. An artificial periosteum comprising a functionalized collagen-containing membrane and a drug-carrier mixture, wherein the drug-carrier mixture comprises at least one therapeutic agent and a calcium-containing carrier mixture.

2. An artificial periosteum according to claim 1, wherein the functionalized collagen-containing membrane is a hydroxyapatite functionalized collagen-containing membrane.

3. An artificial periosteum according to claim 1 or claim 2, wherein the therapeutic agent is a bone active agent.

4. An artificial periosteum according to claim 3, wherein the bone active agent activates osteoblasts.

5. An artificial periosteum according to claim 3, wherein the bone active agent inhibits osteoclasts.

6. An artificial periosteum according to any one of claims 3 to 5, wherein the bone active agent comprises one or more of: PGE1; PGE2; an EP2 receptor agonist; EP4 receptor agonist; an EP2 receptor/EP4 receptor dual agonist; an organic bisphosphonate; a cathepsin K inhibitor; an estrogen or an estrogen receptor modulator; calcitonin; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; a RANKL inhibitor; a bone anabolic agent; a bone morphogenetic agent; Vitamin D or a synthetic Vitamin D analogue; an androgen or an androgen receptor modulator; a SOST inhibitor; platelet-derived growth factor; a pharmaceutically acceptable salt thereof; and a mixture thereof.

7. An artificial periosteum according to claim 6, wherein the organic bisphosphonate is selected from the group consisting of alendronic acid, sodium alendronate, ibandronate, risedronate, zoledronate, zoledronic acid, etidronate, pamidronate, tiludronate, neridronate, and olpadronate.

8. An artificial periosteum according to claim 6, wherein the bone morphogenic protein is selected from the group consisting of BMP-2, BMP-4 and BMP-7.

9. An artificial periosteum according to any one of claims 1 to 8, wherein the drug-carrier mixture comprises a sodium channel blocker, a TRPV1 antagonist, an endothelin antagonist, a bradykinin antagonist, an ASIC inhibitor, a TrkA inhibitor, or a radionuclide.

10. An artificial periosteum according to any one of claims 1 to 9, wherein the drug-carrier mixture comprises an anti-inflammatory agent selected from the group consisting of a NSAID, a corticosteroid, and a cytokine inhibitor.

11. An artificial periosteum according to any one of claims 1 to 10, wherein the drug-carrier mixture comprises an anti-bacterial agent and/or an antifungal agent.

12. An artificial periosteum according to claim 11, wherein the anti-bacterial agent is a cephem, a cephalosporin, a quinolone antibiotic and/or a macrolide.

13. An artificial periosteum according to claim 11, wherein the antifungal agent is fluconazole, clotrimazole and/or itraconazole.

14. An artificial periosteum according to any one of claims 1 to 13, wherein the drug-carrier mixture comprises an anti-cancer agent.

15. An artificial periosteum according to claim 14, wherein the anti-cancer agent is vincristine, doxorubicin, etoposide, gemcitabine and/or methotrexate.

16. An artificial periosteum comprising a hydroxyapatite functionalized collagen-containing membrane and a drug-carrier mixture, wherein the drug-carrier mixture comprises BMP-2 and zoledronic acid.