

**2015 4th TERMIS World Congress
Boston, Massachusetts
September 8–11, 2015**

that can complement BMP activity to maximize osteogenesis while reducing BMP dose requirement. Phenamil is a small molecule that is able to modulate BMP signaling and stimulate osteogenesis. Here, we developed a novel approach combining phenamil and BMP-2 to complement osteogenic activities of BMP-2. The ability of phenamil to promote osteogenic differentiation of adipose-derived stem cells (ASCs) was observed with the addition of different concentrations of BMP-2 *in vitro*. We further evaluated the complementary strategy of phenamil + BMP-2 to enhance bone regeneration in a rat mandibular defect model by using apatite-coated poly(lactic-co-glycolic acid) (PLGA) scaffolds fabricated to slowly release phenamil and BMP-2. Our results showed that phenamil can cooperate with BMP-2 to enhance osteogenic differentiation of ASCs. The enhanced osteogenesis can be explained by synergistic increase of BMP-Smad signaling. After 8 weeks post-operation, the combinatorial group significantly promoted mandibular bone repair compared with the groups treated with phenamil or BMP-2 alone as confirmed by micro-computerized tomography and histology analysis. Importantly, this approach reduced BMP-2 dose but not affected bone healing efficiency. These results suggest that the combinatorial approach using phenamil and BMP-2 may provide more efficient and cost-effective therapy for bone repair.

Acknowledgments: NIH (R01-AR060213, R21-DE021819)

Antibacterial MgO Nanomaterials for Improved Orthopedic Tissue Engineering Applications

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Regeneration of complex orthopedic tissues (such as ligaments, bones, and the tendon-to-bone insertion site) is problematic due to a lack of suitable biomaterials with the appropriate chemical and mechanical properties to elicit formation of tissues with similar structure, organization, and functionality to natural tissues. Additionally, a non-trivial fraction of implanted biomaterials contract bacterial infections, which can lead to implant failure, secondary surgeries, and the spread of infection to other tissues throughout the body. To address these issues, the current study investigated magnesium oxide (MgO) nanoparticles as novel materials to improve orthopedic tissue regeneration and reduce bacterial infection.

Here, MgO nanoparticles and hydroxyapatite (HA) nanoparticles were dispersed within poly-L-lactic acid (PLLA) composites and then tested for their mechanical properties, surface roughness, degradation characteristics, antibacterial properties, and their ability to support the adhesion and proliferation of fibroblasts and osteoblasts.

Results showed for the first time that nanocomposites containing both HA and MgO nanoparticles performed best with respect to osteoblast proliferation and mechanical properties. Increases in alkaline phosphatase expression and vinculin focal adhesions indicated the ability of MgO to enhance the osteogenic properties of HA composites. Further, varying MgO concentrations offered tunable composite degradation kinetics, and the supernatant from degraded composites containing MgO nanoparticles supported greater osteoblast proliferation compared to non-MgO composites. Bacterial experiments with *Staphylococcus aureus* showed that MgO nanoparticles exhibit powerful bactericidal efficacy, suggesting that MgO nanoparticles should be incorporated into scaffolds for orthopedic tissue engineering to improve cell functions and reduce the risk of bacterial infection with limited antibiotics usage.

Glycosaminoglycan Binding Cell Penetrating Peptides for Efficient Gene Delivery

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A major scientific goal is the development of non-viral drug delivery platforms for the delivery of exogenous DNA to cell nuclei. Many of these technologies cannot overcome challenges in low transfection efficiency, cytotoxicity and/or serum-inhibition limiting

in vivo efficacy. If these issues could be resolved then powerful technologies such as *in vivo* cell programming or gene correction could be employed therapeutically.

Cell penetrating peptides (CPPs) are intracellular delivery vehicles that can carry biologically active molecules into cells. In previous work we have shown that when a CPP (8R) was conjugated to a heparan sulphate-glycosaminoglycan (HS-GAG) binding domain (P21) the delivery of a reporter cargo into cells increased by two orders of magnitude. This synergistic increase in transduction was termed GAG-mediated enhanced transduction (GET).

To demonstrate the utility of this protein for delivery of therapeutic molecules we designed and synthesised a DNA-binding GET protein termed P21 LK15 8R. The reporter gene (pSIN GFP) was delivered into cells. Results demonstrated GET-mediated transfection efficiencies of $38.1 \pm 1.8\%$ in serum conditions. We also compared the transfection of GET protein with a commercial transfection reagent Lipofectamine 2000. Cells treated with Lipofectamine 2000 showed inhibited cell growth and lower cell viability than cells treated with P21 LK15 8R. Following a 3 day serial transfection, 4-fold more GFP positive cells were detected using GET gene-transfer compared to Lipofectamine 2000.

In conclusion we have developed a non-cytotoxic and serum-resistant transfection system that could potentially be applied *in vivo* for control of cell behaviour and correction of gene defects.

Saloplastic Membranes as Green Devices for Soft Tissue Regeneration

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Implantable devices must exhibit mechanical properties similar to native tissues to promote appropriate cellular behavior and regeneration. Herein, we report a new membrane manufacture method based on the synthesis of polyelectrolyte complexes (PECs) that exhibit saloplasticity, i.e. variable physical-chemistry using salt as a plasticizer. This is a Green Chemistry approach, as PECs generate structures that are stabilized solely by reversible electrostatic interactions, avoiding the use of harmful crosslinkers completely. Furthermore, natural polyelectrolytes - chitosan and alginate - were used. Upon mixing them, membranes were obtained by drying the PECs at 37°C, yielding compact PECs without resorting to organic solvents. The plasticizing effect of salt after synthesis was shown by measuring tensile mechanical properties, which were lower when samples were immersed in high ionic strength solutions.

Salt was also used during membrane synthesis in different quantities (0M, 0.15M and 0.5M in NaCl) yielding structures with no significant differences in morphology and degradation (around 15% after 3 months in lysozyme). However, swelling was higher (about 10x) when synthesized in the presence of salt. *In vitro* cell studies using L929 fibroblasts showed that cells adhered and proliferated preferentially in membranes fabricated in the presence of salt (i.e. the membranes with lower tensile strength).

Structures with physical-chemical properties controlled with precision open a path to tissue engineering strategies depending on fine tuning mechanical properties and cellular adhesion simply by changing ionic strength during membrane manufacture.

Acknowledgments: Fundação para a Ciência e Tecnologia (grant SFRH/BPD/95446/2013), "Fundo Social Europeu" and "Programa Operacional de Potencial Humano".

Fabrication of Polycaprolactone-Nukbone® (PCL-NKB) Scaffold by 3-D Plotting System for Bone Tissue Engineering

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The fabrication of biological substitutes that maintain improve or restore damaged tissues and organs has been addressed through tissue engineering for many years [1]. Recent advances in 3D-fabrication