FINAL PUBLISHABLE SUMMARY REPORT

Grant Agreement number: 331655

Project acronym: PROTDEL

Project title: Microfluidics-Generated Hydrogel Particles for Protein Delivery

Funding Scheme: FP7-MC-IOF

Project start date: 01/09/2013

The PROTDEL project has been successfully completed. A robust and flexible protein delivery platform with tuneable dosing and release profiles has been established. A microfluidics strategy together with a maleimide-functionalized poly (ethylene glycol) (PEA-MAL) hydrogel system has been used to achieve monodisperse, covalently cross-linked, protease-degradable microgels that cannot be produced using previously reported techniques. Different protease-degradable peptides have been used as crosslinkers (VPM, GPQ(w) and GPQ (A)), in order to control the encapsulation and posterior delivery of specific biological molecules such as growth factors (GFs), by controlling the degradation rate of the hydrogel. In particular, this novel and powerful platform developed by the fellow has been used to promote *in vivo* vascularization via controlled release of the vasculogenic protein VEGF and complete degradation of the microgels that allowed for tissue ingrowth and remodelling. The results of this work have been recently published in Biomaterials. The developed platform is flexible and is at present being optimised to control the delivery of other biological molecules, such as the bone morphogenetic protein (BMP2) for bone healing. In addition, this system, established to produce protease-degradable microgels for protein encapsulation, may also be used for encapsulation of cells and other biological molecules for future applications and has been included in a patent submitted last year. A three month proof of concept project to encapsulate genetically modified bacteria has just been started with internal funding from the University of Glasgow.

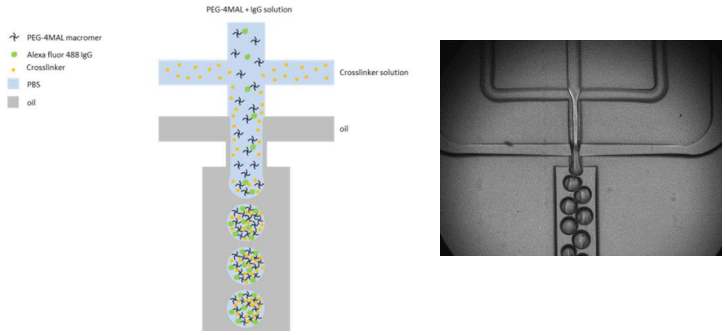

Fig.1 Microfluidic-based hydrogel microparticles for protein encapsulation.

During the development of the Marie Curie project the fellow has received the required training in animal experimentation and she has been trained to master and perform the critical-sized radial segmental defect model in mice. This model was used to rigorously evaluate *in vivo* the role of the synergistic integrin and growth factor signalling - obtained via material-driven FN fibrillogenesis - in bone regeneration. To do so, PEA polymer, which is able to induce the fibrillogenesis of FN in the absence of cells, was used as the material to be implanted. This system allows for the simultaneous and efficient presentation of cell and GF binding domains and showed evident differences in the potential to induce bone regeneration compared to PMA surfaces, a material of similar characteristics which does not induce the fibrillogenesis of FN. The results from this work show the potential of these synergistic signalling microenvironments to promote bone healing. This work has been recently published in Science Advances and has facilitated the funding of new grants for the further development of this technology, including its clinical translation. Moreover, we have demonstrated that the synergistic

signalling provided by this system in not exclusive for BMP2 but is also effective in the presence of other GFs. In particular, the potential of VEGF to promote vascularization *in vivo* has been evaluated in a fat pad model in mice. This work has allowed the researcher to learn and perform another animal model, which has been successfully developed; the results have been recently submitted to Biomaterials.

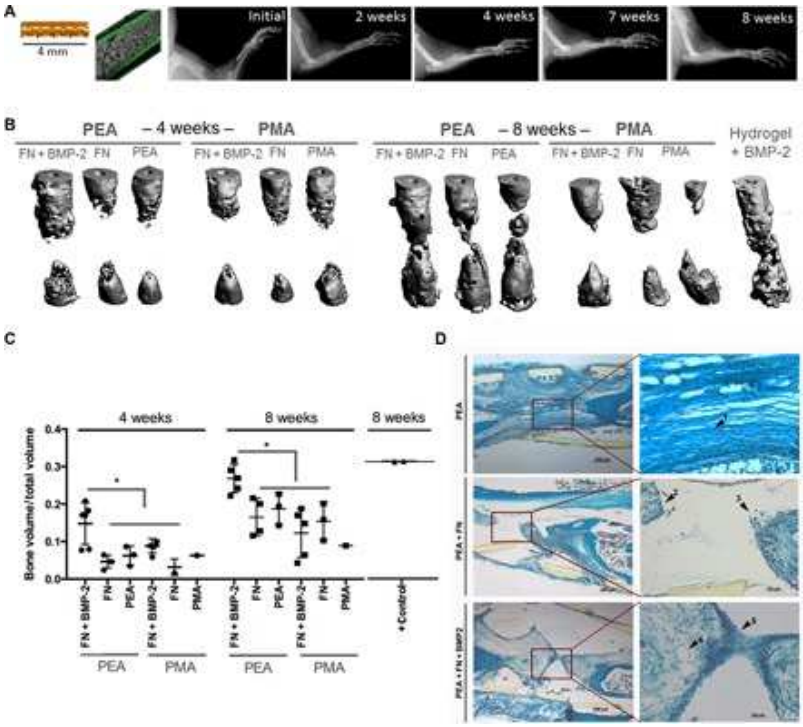

Fig. 2 Bone regeneration in a critical-size defect with very low doses of BMP-2. *Science Advances 2016*

Besides the main objectives of the PROTDEL project, the fellow has also collaborated in another project which allowed the fellow to learn different animal models, providing her with a wider expertise in animal care and surgery. In this study, the osseointegration of stainless steel implants presenting extracellular matrix motifs was evaluated in an animal model of osteoporosis, by implantation in the rat tibia of fibronectin-coated implant screws, and the mechanical fixation of the screws to the bone was measured and compare to the response in healthy rats. The results, which have been published in Biomaterials, show that a simple adsorption of $FN_{III7-10}$ promotes osteogenic differentiation and improves the osseointegration of implant screws. These coatings are easy to apply intra-operatively, even to implants with complex geometries and structures, facilitating rapid translation to clinical settings.

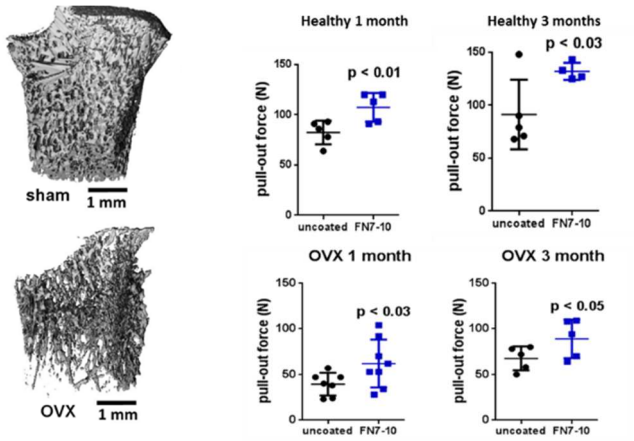

Fig.3 Mechanical fixation of SS screws to bone as determined by pull-out force in healthy and osteoporotic rats. *Biomaterials 2015*