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Biomimetic, biofunctionalised polymer implants to promote *in situ* repair of traumatic and early osteoarthritic cartilage defects

Introduction: We are developing a biomimetic, implantable medical device which is bio-functionalised in a similar conformational and biochemical context to articular cartilage, to promote stem cell homing and retention in the implant and subsequent chondrogenesis and *de novo* cartilage formation. The aim of this study was to assess the efficacy of this technology on the regeneration of articular cartilage *in vitro* and *in vivo.*

Methods: Poly-L-lactic acid (PLLA) random-fibre scaffolds were electrospun and the surface charge was altered by plasma polymerisation using allylamine. The surface-modified scaffolds were treated with heparin and pmol amounts of chondrogenic and stem-cell homing factors. The biofunctionalised scaffold was assessed *in vitro* for its ability to support long-term cell viability and chondrogenesis by bone-marrow MSCs and primary chondrocytes in the absence of other added growth factors or serum. Cell viability was assessed with PrestoBlue® and extracellular matrix (ECM) formation determined by measuring glycosaminoglycan content. The biofunctionalised scaffolds were assessed for *in vivo* activity by implantation into surgically-created 6mm chondral lesions in the medial condyles of sheep, with microfracture immediately before implantation. At 4 and 16 weeks, the treated joints were retrieved and cartilage regeneration assessed macroscopically and histologically.

Results: *In vitro,* functionalisation of the PLLA scaffold with a combination of TGFβ3 and CXCL12 promoted MSC attachment and ingress throughout the implant, and chondrogenic differentiation. Viability of the cells within the construct was maintained in the absence of added chondrogenic factors or serum for at least 5-6 weeks. The MSCs underwent chondrogenesis and produced significantly more ECM ($P \leq 0.05$) than non-functionalised or partially functionalised scaffolds. The scaffolds also promoted chondrocyte attachment, long-term cell viability and ECM formation under the same experimental conditions.

In vivo, implantation of TGFβ3 and CXCL12 functionalised implants showed biological efficacy with regeneration of neocartilage with hyaline features (determined histologically) occurring at 4 weeks with the bio-functionalised implants but the empty defects or control non-functionalised implants.

Conclusions: Bio-functionalisation of PLLA scaffolds with pmol quantities of TGFβ3 and CXCL12 promoted MSC migration and retention in the scaffolds and chondrogenesis with neocartilage tissue regeneration *in vitro* and *in vivo.*