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MSC and Complex Loading Pattern for Cartilage Repair

Research in the use of mesenchymal stem cells (MSCs) to enhance orthopaedic repair has dramatically increased over the last 20 years. The unique properties of MSCs and their natural presence within the bone marrow make them an attractive source of cells for novel therapeutics. When considering the natural repair environment, it is clear that the microenvironment the cells experience plays a major role in the repair response. Within the musculoskeletal system, one of the major drivers of repair is the mechanical load applied to the cells within the defect.

When developing new therapies *in vitro*, static culture is the most commonly used method. However, it is clear that due to the critical role mechanics plays *in vivo*, a more physiological loading regime in vitro would be most appropriate and this can be achieved by the use of bioreactors. Using a multiaxial load bioreactor system, we have been investigating the effect of mechanical stimulation on human stem cell differentiation. Performing studies in the absence of growth factors, specifically Transforming growth factor β (TGF β), allows the direct effect of the mechanical strain applied to be elucidated. Our bioreactor system allows for the application of shear, compression or a combination of both stimuli to establish the phenotypic changes induced within MSCs. In particular, the effect of the various mechanical stimuli on chondrogenic differentiation will be discussed and compared to responses seen in chondrocytes.

As a model system, human bone marrow derived MSCs are embedded in a fibrin gel, which is then retained in a macroporous biodegradable polyurethane (PU) scaffold. This system provides a naturally occurring support matrix (fibrin), while allowing for cyclical load to be applied due to the resilience of the PU scaffold. Neither compression alone, nor shear

alone can induce a change in MSC phenotype within this system. However, we have demonstrated that a combination of compression and shear is able to induce chondrogenic differentiation and this is due to increased endogenous expression of TGF β from the loaded cells. Finite Element modelling of the bioreactor system demonstrated that the degree of principle component strain was the main driving force in this system.

Using this multiaxial load bioreactor system we are able to investigate novel treatments and therapies *in vitro*, under physiologically relevant kinematic load. In addition, potential rehabilitation protocols to be used after cell therapy in cartilage repair can also be investigated.