Lay progress report Dec 2016

Project & Lead centre	
Principle Investigator	Floris Lafeber / Simon Mastbergen
Leading centre	UMC Utrecht
City	Utrecht
Country	Netherlands

Degenerative joint diseases such as OA are a great and growing socio-economic problem where the only definitive therapy has been joint replacement surgery. There is an ongoing exponential increase in knee joint replacements together with a significant decline in the age at which joint replacements are performed (Bijlsma J, *Lancet* 2011). Consequently, this leads to high numbers of revision surgeries, which are both costly and less beneficial. (Bitton R, *Am J Manag Care* 2009). Clearly effective treatments that can postpone, or even avoid, this final option are needed.

The last year we have given several presentations regarding joint distraction, at both international and national conferences. Examples, are presentations at the annual meetings at the ORS 2016, OARSI 2016, and ICRS 2016 as well the Dutch Arthritis Foundation and national meeting of the Dutch Rheumatology Association (NVR). Within these presentations we underline the importance of unravelling the mechanism of joint repair and this project.

Worldwide, the general opinion is that OA joint cartilage cannot repair itself, as it has a limited number of cells in an abundant amount of extracellular matrix that is not vascularized. Working against this dogma, we have demonstrated that application of unloading by knee joint distraction (6-8 wks) leads to prolonged (>5 yrs currently) intrinsic cartilage repair in combination with meaningful clinical efficacy (Mastbergen S, *Nat Rev Rheumatol* 2013; Intema F, *ARD* 2011; Wiegant K, *OAC* 2013, van der Woude Knee 2016, PLos One 2016). As this intrinsic cartilage repair activity is unique, this provides for the first time the opportunity to unravel and identify the mechanisms that are essential for this cartilage repair.

The present proposal then aims at identifying the cells and metabolites that are present or induced by joint distraction to better understand and further refine joint distraction treatment. The astonishing cartilage repair activity as observed by joint distraction cannot be solely the result of the matrix synthesis by the resident chondrocytes. It is anticipated that intrinsic mesenchymal stem cell (MSC) activity plays a crucial role in this observed cartilage repair activity. We discovered synovial fluid (SF) in OA contains MSCs, of which the number is elevated in the early stages of OA (Churchman S, *Arthritis Rheumatism* 2012; Jones E, *Arthritis Rheumatism* 2004). The discovery of this resident population of highly proliferative MSCs in SF whereby such cells have reproducibly good chondrogenic activity (Churchman synovium, synovial fluid and subchondral bone marrow. Activation and migration of these MSC populations may play a key role in repair. Pilot data (UK) using human OA joints showed an increased MSC proliferative response in subchondral bone areas directly adjacent to the denuded cartilage. Moreover, our *in vitro* pilot (UK) work demonstrated that the SF biochemical composition influences MSC cartilage adherence. Several mediators (cytokines, growth factors, lubricants, etc) as well as inflammatory cell subsets will be change by joint

distraction as well. Within the consortium extensive expertise on delineating these 'soluble' and 'inflammatory' components of joint distraction in the OA joint (Fr) exist.

The proposed project will unravel the still unknown mechanisms that lead to cartilage repair (as observed in response to joint distraction) and reveal the mechanisms by which MSCs are involved in this repair activity, how intra articular soluble mediators influence their activity, and how their role can be optimized. Acquiring this knowledge will cross new frontiers to optimize, refine and provide solid scientific rationale for an exciting and tangible novel treatment of OA.

S, *A&R* 2012) supports the concept that such MSCs, having a direct access to the damaged cartilage areas, and so may be key players in the reparative process as a result of joint distraction. Crucially, our collaboration (UK/NL) has recently shown that SF resident MSCs adhere to sites of cartilage injury in a canine OA model.

It is anticipated that joint distraction provides the appropriate biomechanical and biochemical intra-articular milieu, facilitating MSC attachment and their cartilage repair activity. Our collaborative (NL/UK) pilot experiment on dogs already suggested that joint distraction (decreased mechanical stresses) facilitates adherence of MSCs to the cartilage surface. There are several MSC niches adjacent to articular cartilage including those in joint fat tissue, synovium, synovial fluid and subchondral bone marrow. Activation and migration of these MSC populations may play a key role in repair. Pilot data (UK) using human OA joints showed an increased MSC proliferative response in subchondral bone areas directly adjacent to the denuded cartilage. Moreover, our *in vitro* pilot (UK) work demonstrated that the SF biochemical composition influences MSC cartilage adherence. Several mediators (cytokines, growth factors, lubricants, etc) as well as inflammatory cell subsets will be change by joint distraction as well. Within the consortium extensive expertise on delineating these 'soluble' and 'inflammatory' components of joint distraction in the OA joint (Fr) exist.

The proposed project will unravel the still unknown mechanisms that lead to cartilage repair (as observed in response to joint distraction) and reveal the mechanisms by which MSCs are involved in this repair activity, how intra articular soluble mediators influence their activity, and how their role can be optimized. Acquiring this knowledge will cross new frontiers to optimize, refine and provide solid scientific rationale for an exciting and tangible novel treatment of OA.