ARGOSPINE THESIS AWARD

Novel regenerative strategies for the treatment of intervertebral disc herniation

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Lumbar discectomy is an effective therapy for neurological decompression in patients suffering from sciatica due to a herniated nucleus pulposus (NP). Discectomies however, do not deal with the damaged intervertebral disc (IVD) and high numbers of patients suffer from persisting postoperative low back pain. This has resulted in many strategies targeting the regeneration of the NP. In this thesis we developed a novel tissue engineering strategy to treat patients suffering from a herniated intervertebral disc (IVD). Our goal was develop a regenerative therapy for the IVD that can be used in a one-step surgical procedure in adjunct to a discectomy. The thesis started with the optimization of scaffold materials. Recently, it was appreciated that the mechanical properties of scaffolds might regulate cell behaviour. In chapter 2 we matched the stiffness of dense collagen type I scaffolds to the nucleus pulposus (NP). We also showed that a standard treatment with γ -sterilization resulted in an increase of stiffness, but also in a more brittle behaviour and a reduced swelling capacity. In chapter 3 we matched the stiffness of alginate scaffolds to the NP and studied the effects of different stiffnesses on native cells. The biosynthetic phenotype of the cells was preserved in alginate, but no differences were found between the various scaffold densities most likely due to the poor adhesiveness of the cells to alginate. In addition, we found that the stiffness of alginate scaffolds rapidly declined upon incubation in medium. If cells from surrounding tissues are able to migrate into scaffolds in vivo, expensive and time consuming pre-seeding techniques are not necessary. This new concept, sometimes referred to as "in situ" seeding is explored in chapter 4. We found that native cells are capable of migrating into dense collagen scaffold in vitro and the migration distance was density dependent and was higher for NP compared to annulus fibrosus (AF) cells after 4 weeks of culturing. We also observed a lag phase, before migration occurred. Although the densities used in this study were lower (1.5 and 3%) compared to the density shown to mimic the NP (23%), we proved that native cells are capable of invading dense collagen scaffolds and the in situ seeding concept seems viable. In chapter 5 we summarized and discussed all available literature on annulus fibrosus (AF) closure techniques. We found that several attempts to repair, support or regenerate the AF have been studied, but a successful clinical application is still far away. In general, tissue engineering strategies lack a vision on the final clinical application and repair therapies lack scientific evidence. In chapter 6 we tested annulus closure devices

(ACD's) intended to be used in our goat nucleus replacement model. We showed that ACD's with four barb rings could withstand the highest axial load and the increased range of flexion-extension and lateroflexion due to the discectomy was restored after implantation of an ACD and collagen implant in cadaveric lumbar spines. The positive results were confirmed in a goat pilot study after two weeks follow up. However, in a second pilot study most ACD's revealed signs of destruction and/or displacement after 6 weeks follow-up. We also found two endplate reactions extending into the subchondral bone, most likely due to continuous friction of the ACD's between the vertebrae. Finally, we present the results of the collagen scaffold that was used in adjunct to ACD's in the goat study. After 6 weeks the disc height index in goats treated with the collagen implants was not significantly decreased compared to untreated control levels. Levels that received a discectomy or ACD alone did show a significant decrease in disc height. Macroscopy revealed that the dense collagen was not yet integrated with the NP tissue and therefore lost during sawing and preparation for histology. Histologic and magnetic resonance imaging score were not useful to evaluate the results after 6 weeks follow up. ●

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Johannes Leendert (Harry) Bron was born on January 18th, 1980 in Leerdam, The Netherlands. After graduating from high school (Heerenlanden College, Leerdam) in 1999, he studied Medicine at the Vrije Universiteit Amsterdam. During his medical internships he participated in orthopaedic research with Prof. Dr. P.I.J.M. Wuisman (†) at the department of Orthopaedic Surgery of the VU University Medical Center Amsterdam. After receiving his medical degree (cum laude) in 2005, he started to work as an orthopaedic resident at the same department. In 2006 he started his PhD-project focusing on novel regenerative strategies of the intervertebral disc as described in this thesis (supervisors: Prof. Dr. B.J. van Royen, Prof. Dr. ir. T.H. Smit and Prof. Dr. G.H. Koenderink). The project has resulted in several publications and this thesis. As part of his training in Orthopaedic surgery he started a residency in General Surgery at the Spaarne Ziekenhuis in Hoofddorp (Head: Dr. G.J.M. Akkersdijk) in 2010. In 2012 he continued his orthopaedic surgery training at the VU University Medical Center (Head: Prof. Dr. B.J. van Royen).