McKee C, et al., J Stem Cell Res Dev 2021, 7: 064
DOI: 10.24966/SRDT-2060/100064

HSOA Journal of
Stem Cells Research, Development and Therapy

Commentary

A Combinational Approach Using Cell Therapy, Tissue Engineering, and Distracting Device for the Treatment of Degenerative Disc Disease

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Commentary

The Intervertebral Disc (IVD) is a fibrocartilaginous tissue instrumental in spine flexibility, allowing for the bending and twisting motion between vertebral bodies. Degenerative Disc Disease (DDD) results from the complex and chronic deterioration in IVD organization, structure, and function [1]. DDD has been implicated in the majority of cases of chronic Lower Back Pain (LBP) [2]. LBP is one of the most prevalent and debilitating musculoskeletal diseases, affecting nearly 80% of Americans during their lifetime [3]. Consequently, IVD degeneration accounts for around 25%-30% of all direct and indirect healthcare costs in North America and Europe [4]. In the United States alone, an estimated $84.1 billion to $624.8 billion has been spent annually for the treatment of LBP. In addition, a loss of between $7.4 billion to $28 billion annually has been reported from diminished work productivity [5]. As such, there is a great deal of interest in elucidating the etiology of DDD and relieving the expansive societal burden associated with DDD. Toward this end, it is important to understand the biology and function of IVD as well as the intrinsic and extrinsic factors associated with degeneration.

The IVD is composed of an inner highly hydrated Nucleus Pulposus (NP) tissue, which is surrounded by an outer collagen-rich Annulus Fibrosus (AF) and flanked by cartilaginous endplates [6]. The AF is characterized by its high tensile strength [7], providing protection to the gelatinous NP, which is responsible for the shock-absorbing and weight-bearing cushioning of spinal loads [8]. Multiple factors have been implicated in IVD degeneration, including altered mechanical loading, nutrient deficiency, changes in cellular deposition and hereditary factors [9-12]. Degenerative changes in the NP are characterized by the replacement of NP progenitors, notochordal disc cells, with Chondrocyte-Like Cells (CLCs), resulting in the loss of osmotic properties and Extracellular Matrix (ECM) integrity, leading to the formation of fibrocartilage tissue [13]. These age-related cellular and ECM changes negatively impact the biomechanical capabilities of the IVD, and subsequent trauma can lead to further structural damage of the tissue [8]. Due in part to a lack of vascularization and cellularization [14], cells within the NP account for only approximately 1% of the total volume of the IVD [13] and as a result, the IVD has little to no regenerative capacity [7].

Currently, there is no effective treatment for DDD and/or chronic LBP. In general, treatments address symptomatic pain management using analgesics and physiotherapy [7,15]. In severe cases, aggressive surgical procedures such as discectomy and spinal fusion are performed; however, these interventions are highly invasive and often lead to reduced IVD and spine function [7]. Therefore, recent efforts have focused on cell therapy to aid in IVD regeneration by addressing the underlying cause of DDD. While pre-clinical and clinical studies have indicated that cell transplantation is feasible, debate on the optimal cell source as well as the mechanism/vehicle of delivery still exists [16-18].

Early attempts at treating DDD using allogenic articular chondrocytes isolated from juvenile tissue showed promising results with improvement in reported LBP in small-scale preliminary studies, although the majority of radiographic measurements did not indicate significant improvement [19]. In early phase I clinical trials, transplantation of NOVOCART Disk plus, autologous chondrocytes derived from IVD cells, indicated no beneficial improvement but no adverse effects; phase II studies are estimated to be completed in 2021, following 5 years of observation, and may provide more information on long-term functional improvement [20]. However, a major limitation of these studies is the use of chondrocytes cells, which are difficult to isolate and expand to the numbers needed for therapeutic applications [21]. Additionally, chondrocytes, which are considered to be end differentiated cells are not felt to contribute to the production of extracellular proteoglycans or Glycosaminoglycans (GAG), which is largely responsible for the water holding capacity of the IVD [22]. Therefore, the effectiveness of these cells in restoring the degenerated desiccated disc to normal functional hydration is

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Citation: McKee C, Perez-Cruet M, Chaudhry GR (2021) A Combinational Approach Using Cell Therapy, Tissue Engineering, and Distracting Device for the Treatment of Degenerative Disc Disease. J Stem Cell Res Dev Ther 7: 064.

Received: February 11, 2021; **Accepted:** February 18, 2021; **Published:** February 25, 2021

questionable. Consequently, numerous clinical studies have focused on Mesenchymal Stem Cells (MSCs). These cells are multipotent and self-renewing stem cells that can be isolated from a variety of adult tissues [23]. In general, the majority of clinical trials have utilized bone marrow derived MSCs (BM-MSCs) for transplantation into degenerated IVDs and have reported outcomes ranging from no palliative relief to reduced pain and improved disc hydration [24-27]. The inconsistency of these results may be in part due to the variability of isolated BM-MSCs. MSCs from adult sources are often invasively isolated in low quantities with cell quality correlated to donor age [28,29]. As a result, we have focused our research on the therapeutic use of primitive MSCs isolated from perinatal tissues [30,31]. These cells can be non-invasively harvested from discarded umbilical cord and placenta following birth and have shown enhanced growth potential, allowing for the production of the large number of cells needed for preclinical and clinical studies.

In our lab, we have isolated primitive MSCs from a unique niche of the umbilical cord tissue, which has shown high proliferative capability compared to BM-MSCs [31]. These umbilical cord derived MSCs are capable of differentiation into chondroprogenitor cells [30-32]. In fact, we observed that differentiation of primitive MSCs into chondroprogenitor cells prior to transplantation improved their regenerative capacity in a rabbit model of DDD [32]. Transplanted cells survived, integrated, and dispersed in the damaged areas of the NP and were functionally active expressing human chondrogenic genes, *SOX9*, *ACAN* and *COL2* [32]. These chondroprogenitor cells also produced NP matrix proteins including sulfated GAG (sGAGs), and improved histological and water content properties of the degenerated IVD [32]. In a subsequent study, we further optimized *in vitro* differentiation of primitive MSCs into NP-like Cells (NPCs), expressing chondrogenic and acknowledged NP specific markers [33-35] including, *FOXF1*, *KRT19*, *PAX6*, *CA12* and *COMP* [36]. In agreement with our previous studies, differentiated cells showed improved efficacy over MSCs when injected into degenerated rabbit IVDs. NPC transplantation enhanced ECM accumulation and cellularity in the augmented NP, which exhibited improved physicochemical characteristics including sGAG, NP content, and disc hydration [36]. Overall, these findings further emphasize the importance of both cell source and lineage differentiation in the regeneration of damaged IVDs by addressing the etiology of the disease. However, the overall success of cell transplantation in clinical studies has been shown to also be limited by the propensity of cell leakage from the site of injection [37-39] and failure to reestablish mechanical function by restoration of disc height [7,15,40].

Consequently, tissue engineering techniques utilizing biocompatible materials have recently garnered enthusiasm due to their ability to promote mechanical stability in degenerated IVDs in DDD animal models [41]. Transplantation of whole xenograft IVD constructs require highly invasive medical interventions, which can result in additional structural IVD damage [42-44]. Therefore, we and others have focused our studies on the use of injectable hydrogel scaffolds, which mimic the fully hydrated native NP and can form at the site of injury [2,15,45]. It is imperative to employ biomaterials with the mechanical strength to support spine loading, as well as support IVD cell growth and differentiation.

Using an *ex vivo* model of DDD, we have demonstrated the successful injection of cells using self-assembling scaffolds comprised of two synthetic and biocompatible Polyethylene Glycol (PEG) polymers functionalized with acrylate (PEG-4-Acr) and thiol end (PEG-4-SH) group [46]. These polymers self-assemble via Michael addition reaction forming chemically cross-linked hydrogels, capable of forming at the site of injection *in situ*. Our results showed that the PEG-4-Acr/PEG-4-SH self-assembling scaffolds promoted retention of injected cells in the IVD without leakage. More importantly, we observed that transplantation of MSCs with the PEG-4-Acr/PEG-4-SH scaffolds improved MSC differentiation into NPCs. This confirmed our *in vitro* studies, which showed that 3-D culture of MSCs in the PEG self-assembling scaffolds promoted differentiation into a NP lineage without the need for inductive media [46]. Injection of MSCs with the self-assembling scaffolds also resulted in significant improvement in structural integrity and cellularity of the NP of degenerated IVD explants when compared to cells or scaffolds alone. IVD explants injected with MSCs using the self-assembling scaffolds displayed higher ECM production of proteoglycans, glycoproteins, and sGAG at levels resembling healthy NP. Transplantation of cells together with the self-assembling scaffold also led to upregulation of NP specific markers, including *FOXF1*, *K19* and *VIMENTIN*, known to be associated with NP cells.

Overall, these findings support the use of a novel multi-pronged treatment strategy, allowing for 1) transplantation of highly proliferative and primitive MSCs with minimal manipulation *in vitro*; 2) increased cell retention upon injection at the site of injury; and 3) highly specified differentiation into NPCs capable of producing NP markers and ECM for regeneration of damaged IVD tissue. Additional clinical studies are warranted to optimize the mechanical properties of injectable scaffolds and its effect on disc height and palliative treatment.

While the self-assembling scaffold may mimic the elastic and hydrated properties of native NP tissue, it may not provide enough mechanical support to allow for complete restoration of disc height in degenerated IVDs. This could be addressed with the help of a pedicle screw based minimally invasive distractive medical devices to provide the space needed to allow for both successful cell integration and regeneration of disc. This proprietary device (Annulo™) was designed to allow for a gradual distraction of the disc space. By applying a motion sparing distractive forces to the disc, over time the disc can be restored to its natural height, mimicking the action of tissue expanders, which allow for the gradual generation of new skin for skin grafting procedures when placed under the skin [47,48]. After the disc height is restored, NP derived MSC scaffolds can be injected into the NP to restore its function, therefore returning the degenerated collapsed disc to its normal functional capacity. As such, the temporary use of an IVD distracting device, such as the Annulo™ technology, may supplement cellular therapy and aid in the restoration of both the biological and mechanical function of the IVD. Such inter-transdisciplinary approaches should be investigated in preclinical and clinical studies, thus facilitating bench-to-basic science research in collaboration with clinical product development to improve patient outcomes. These studies could provide proof-of-concept for combinational use of self-assembling scaffolds for the delivery of cells and a distracting device via minimally invasive surgery to maintain disc height, thus providing a regenerative environment for the treatment of DDD.

Acknowledgements

The study was supported by the OU-WB Institute for Stem Cell and Regenerative Medicine (ISCRM), Oakland University, and Michigan Head and Spine Institute. C. McKee received the Provost Graduate Research Award from Oakland University for this project.

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