Epiphyseal Chondro-Progenitor Cells Combined with Microfracturing for Resurfacing Full Thickness Chondral Defects - A Pre-clinical 3-months GLP Safety Study in Goats


1Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland, 2University of Zurich Tierspital, Zurich, Switzerland, 3Lausanne University Hospital, Lausanne, Switzerland.

Disclosures:

Introduction: Bone marrow stimulation or microfracture (MF) is the most widely used surgical technique to repair cartilage tissue injuries. While repair tissue is built relatively quickly, the MF procedure leads to the formation of a fibrocartilagenous scar tissue. Another major pitfall of MF is the instability of the mesenchymal blood clot formed. Autologous Matrix Induced Chondrogenesis (AMIC) can be used to stabilize the blood clot with a membrane, which can be glued in place using tissue sealant. The clinical superiority of AMIC compared to standard MF however has not yet been determined by randomized trials. The use of autologous therapeutic cells in the case of Autologous Chondrocyte Implantation (ACI) still lags behind MF in the number of procedures performed to date, despite the many generations of ACI improvements and the inherent limitations of MF, probably due to the unreliable expansion of adult chondrocytes and the unpredictability of adult stem cell preparations. As such, we have endeavored to combine the matrix-stabilizing technique with novel therapeutic cells, which may effectively interact with reparative cells from the bone marrow and transform the repair response to a regenerative response.

We have previously reported the reliable expansion and characterization of a clinical-grade human epiphyseal chondro-progenitor (ECP) cell bank from a single tissue donation. Aimed for allogenic off-the-shelf implantation, ECPs exhibited remarkable homogeneity and stability in expansion as well as a spontaneous chondrogenic potential and an inherent resistance to multilineage differentiation [1]. Indeed, ECPs provide the stability, reliability and traceability required by allogenic cell therapy.

We have conducted a GLP-grade pre-clinical 3-months safety study in goats to assess the effect of implanted ECPs in a full thickness cartilage defect. ECPs were delivered within a collagen-based matrix. The cell-laden construct is delivered in combination with MF to direct new tissue repair and remodeling. We present here the findings from our 3-months pre-clinical study, focusing on the safety of ECPs, the feasibility of the proposed treatment protocol as well as early indications of regeneration.

Methods: This study was performed in compliance with Principles of Good Laboratory Practice (OECD, C(97)186/Final). All animal experiments were conducted according to Swiss laws of animal protection and welfare and authorized by the cantonal ethical committee (license 174/2012). Eight female Saanen goats were randomized to two treatment groups. Six goats in the ECP group received ECPs seeded in Chondro-Gide® collagen matrix (Geistlich, Switzerland) over MF in full thickness chondral defects. Two goats in the control group received saline soaked Chondro-Gide® matrix over MF (Figure 1). Full thickness chondral defect were performed in medial and lateral condyles of the stifle joint. Animals were sacrificed 3 months after the surgery. Organ and tissue samples were processed to screen for traces of human cells as well as potential histological abnormalities. Magnetic Resonance Imaging was performed on operated stifles to detect subchondral bone sclerosis and bone marrow edema. Macroscopic, histological and immunohistochemical assessments were performed to evaluate the quality of early repair as well as that of the surrounding cartilage and subchondral bone.

Results: At the early 3-month time point, the macroscopic state of repair as well as subsequent subchondral bone sclerosis and bone marrow edema showed no statistically detectable difference compared to control. A trend was however observed in cartilage tissue surrounding the defects with the ECP group exhibiting healthier, better preserved surrounding cartilage compared to controls (Figure 2). Tracking ectopically engrafted human cells did not reveal pathological observations of any kind.

Discussion: ECP implantation in combination with AMIC may provide necessary protective cues to maintain joint homeostasis during repair. Whether ECPs are more likely to work as chaperones of repair or builders of new tissue, results from the 3-months study highlights their safety. The proposed implantation protocol provides the operating room staff with enough flexibility without requiring much pre-planning or the need for additional expensive equipment in the operating room. The results obtained will help inform the design of a long-term investigation attempting to achieve functional cartilage regeneration.

Significance: As a first step in defining a novel strategy for cartilage regeneration, we have conducted a GLP-grade 3-months pre-clinical safety study in goats to assess the effect of implanted therapeutic progenitor cells (Epiphyseal Chondro-Progenitors) in a
full thickness cartilage defect. The results highlight the safety of Epiphyseal Chondro-Progenitor cells, the feasibility of the proposed treatment protocol as well as sheds light on early indications and mechanisms of regeneration.

Acknowledgments: These studies were funded by the Swiss National Science Foundation (No. 205320_132809), the Interinstitutional Center for Translational Biomechanics EPFL-CHUV-DAL, and in part by the Sandoz Family Foundation and the S.A.N.T.E Foundation.

CTR group
n = 2

Matrix + MF

ECP group
n = 6

Matrix + ECP + MF

- Fibrin Glue
- Microfracturing (MF)
- Cartilage
- Matrix (ChondroGide ®)
- ECP Cells
- Subchondral bone

Figure 1: Study design showing defects in the CTR group receiving collagen matrix and the ECP group receiving the matrix seeded with ECPs.
Figure 2: The macroscopic state of the defect filling was graded as well as the health of cartilage tissue immediately surrounding the defect zone within 4mm (Zone 1) and the tissue beyond the 4mm demarcation (Zone 2).