# Successes and hurdles in the translation of tissue engineered products for cartilage repair in clinical trials: focus on regulatory perspectives

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**INTRODUCTION:** Spontaneous healing of cartilage injuries is poor. Untreated cartilage defects are associated with pain and disability, and predispose to osteoarthritis. Current therapies, including innovative autologous cell-based treatments (exclusively based on articular chondrocytes), cannot predictably and reproducibly restore cartilage structure and function[1]. Based on several years of basic and pre-clinical research supporting the use of nasal chondrocytes as a suitable cell source for the regeneration of native cartilage, different clinical trials have been initiated by our group.

**METHODS & RESULTS:** Autologous nasal chondrocytes are isolated from a small nasal septum cartilage biopsy harvested in minimally invasive out-patient procedure. Nasal chondrocytes are expanded in vitro and then cultured onto a collagen membrane in chondrogenic medium to promote the deposition of abundant extracellular matrix (Fig. 1).

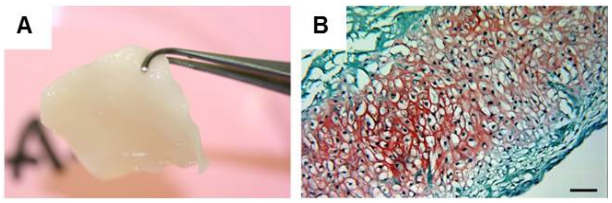


*Fig. 1: Macroscopic (A) and histological (B, Safranin-O) picture of tissue engineered cartilage graft based on nasal chondrocytes.*

In a Phase I clinical trial, tissue-engineered cartilage grafts were used for the reconstruction of nasal alar lobules, leading to a durable and stable repair with restoration of function and aesthetically satisfactory outcomes[2]. Based on subsequent *in vitro* and pre-clinical studies, a further Phase I clinical trial was conducted in which autologous nasal cartilage tissues were engineered for the treatment of full-thickness cartilage defects in the knee joint, providing evidence of engraftment of the graft within the defect site[3]. While the Phase I trials have demonstrated the safety and feasibility of the approach, a multicenter Phase II clinical trial is being initiated to finally prove efficacy of the tissue-engineered nasal cartilage grafts for the treatment of cartilage lesions in the knee [www.biochip-h2020.eu]. In parallel, innovative bioreactor-based platforms that automate, standardize, and scale up the production process are developed with the aim to foster exploitation of tissue-engineered products for widespread clinical use[4] [www.biocomet.eu].

**DISCUSSION & CONCLUSIONS:**
The translation of research scale production models into clinically applicable manufacturing designs that are compliant with regulatory requirements (e.g., GMP, GDP, GCP) and economically sustainable poses major challenges to bring tissue-engineered products into routine clinical practice. Successes, struggles and setbacks have characterized our way and will be discussed: from the bench to clinical trials, from single to multiple centres in Europe with centralized GMP production, from conventional to automated manufacturing. Close collaboration among clinicians, academic institutions, industrial partners, and regulatory agencies is being crucial to expedite the route to successful clinical translation of engineered tissue products.

**REFERENCES:** [1]P. Niemeyer, J.M. Pestka, P.C. Kreuz, et al (2010) *Knee Surg Sports Traumatol Arthrosc* 18:1122-7. [2]I. Fulco, S. Miot, M.D. Haug, et al (2014) *Lancet* 384:337-46. [3]K. Pelttari, B. Pippenge, M. Mumme, et al (2014) *Sci Transl Med* 6:251ra119. [4]M.A. Asnaghi, T. Smith, I. Martin, et al (2014) Bioreactors: enabling technologies for research and manufacturing in *Tissue Engineering 2nd Ed* (eds C. Van Blitterswijk and J. De Boer) Elsevier.

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