Review

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Advanced cell therapies for articular cartilage regeneration

Catarina Madeira[1], Aruna Santhagunam[1], João B. Salgueiro[2], and Joaquim M.S. Cabral[1]

[1] Department of Bioengineering and Institute for Biotechnology and Bioengineering, Instituto Superior Técnico, Universidade de Lisboa, Avenida Rovisco Pais, 1049-001 Lisboa, Portugal
[2] Centro Hospitalar de Lisboa Ocidental, Entidade Pública Empresarial (EPE) Hospital São Francisco Xavier, Estrada do Forte do Alto do Duque, 1449-005 Lisboa, Portugal

Advanced cell-based therapies are promising approaches for stimulating full regeneration of cartilage lesions. In addition to a few commercially available medicinal products, several clinical and preclinical studies are ongoing worldwide. In preclinical settings, high-quality cartilage tissue has been produced using combination strategies involving stem or progenitor cells, biomaterials, and biomolecules to generate a construct for implantation at the lesion site. Cell numbers and mechanical stimulation of the constructs are not commonly considered, but are important parameters to be evaluated in forthcoming clinical studies. We review current clinical and preclinical studies for advanced therapy cartilage regeneration and evaluate the progress of the field.

Current advanced therapies for cartilage regeneration

Articular cartilage is an avascular tissue with a highly complex structure that has only limited capacity for self-repair because it mainly consists of chondrocytes encapsulated in a dense matrix of proteoglycans and collagens. Focal chondral or osteochondral lesions in the knee caused by traumatic injuries often result in pain and swelling, frequently developing into larger, degenerative lesions and osteoarthritis (OA). Severe focal injuries in cartilage are currently treated by one of the three main types of surgery: bone marrow stimulating techniques, mosaicplasty, and cell based therapies.

The first generation of cell based therapy, autologous chondrocyte implantation (ACI), was introduced in 1987 by Brittberg and published in 1994 following FDA consent for clinical studies [1]. In October 2009, the first cell based product to obtain market authorization from the European Medicines Agency (EMA) as an Advanced Therapeutic Medicinal Product (ATMP) was ChondroCelect from Tigenix (Belgium). In the USA, Carticel from Genzyme is the only FDA-approved cell therapy product for regenerating articular cartilage. ChondroCelect and Carticel therapies may eventually involve the use of a type I/II collagen hydrogel patch, such as ChondroGide (Geistlisch) or CaReS (Arthro kinetics), instead of the periosteal flap to confine the *ex vivo* expanded chondrocytes to the lesion site. Histological comparison of tissue formed after using periosteal or Chondrogide® during ACI pointed towards the superiority of the latter [2].

In addition, clinical trials are underway to evaluate hydrogels as matrices for supporting autologous chondrocyte implantation. This strategy involves culture of chondrocytes on a matrix, followed by implantation at the lesion site, a procedure known as matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI). MACI™, a proprietary version of the technology from Genzyme, has been approved for clinical trials by the FDA. Several proprietary biomaterials, such as Novocart 3D [3], Neocart [4], and Chondron [5], which are approved in clinical trials for use without cells, are being considered by their respective companies for implantation with autologous chondrocytes according to the MACT strategy (Table S1 in the supplementary material online). In a different approach, Chondrofix [6] and DeNovo NT [7], hyaline cartilage allografts for treatment of severe and initial articular cartilage lesions, respectively, are being considered as tissue engineering (TE) products. As recently reviewed [8], these products have great potential because they can enable multifactorial mimicry, which has not yet been achieved using man-made biomaterials.

In January 2012 the Korean FDA approved the manufacture and sale of Cartistem as an allogeneic stem cell drug for the treatment of OA. This product uses mesenchymal stem or progenitor cells (MSC) isolated from umbilical cord blood (UCB). Despite great interest from the worldwide advanced therapy community, no results have yet been reported in peer-reviewed journals.

Clinical trials using advanced therapies

Clinical translation of cell based therapies is challenging not only because it requires costly and reliable cell manufacturing but also because delivery to the patient is complex. Strategies consisting of a single ATMP are essentially those in which cells, a matrix, or vectors carrying genes are injected intra-articularly or are loaded into the lesion site. Combination strategies consider the simultaneous use of these elements before implantation: cells embedded in a hydrogel or previously cultured on a scaffold (Figure 1A), genetically modified cells (Figure 1B),

Corresponding author: Madeira, C. (catarina.madeira@tecnico.ulisboa.pt).
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a matrix embedded with gene vectors (gene activated matrix) (Figure 1C), or a combination of all three elements (Figure 1D). Most of these strategies are now in clinical trials for cartilage regeneration (Table S1), with the exception of the implantation of a gene-activated matrix on the lesion site, which has been evaluated only in preclinical settings [9]. Over the past decade, several authors have systematically reviewed the results of randomized controlled trials (RCT) or Level IV studies using ACI [10–12], both ACI and MACT [13], and stem cell therapies [14–16].

Ideally, any therapy should be as simple as possible. However, in the case of articular cartilage lesions, especially

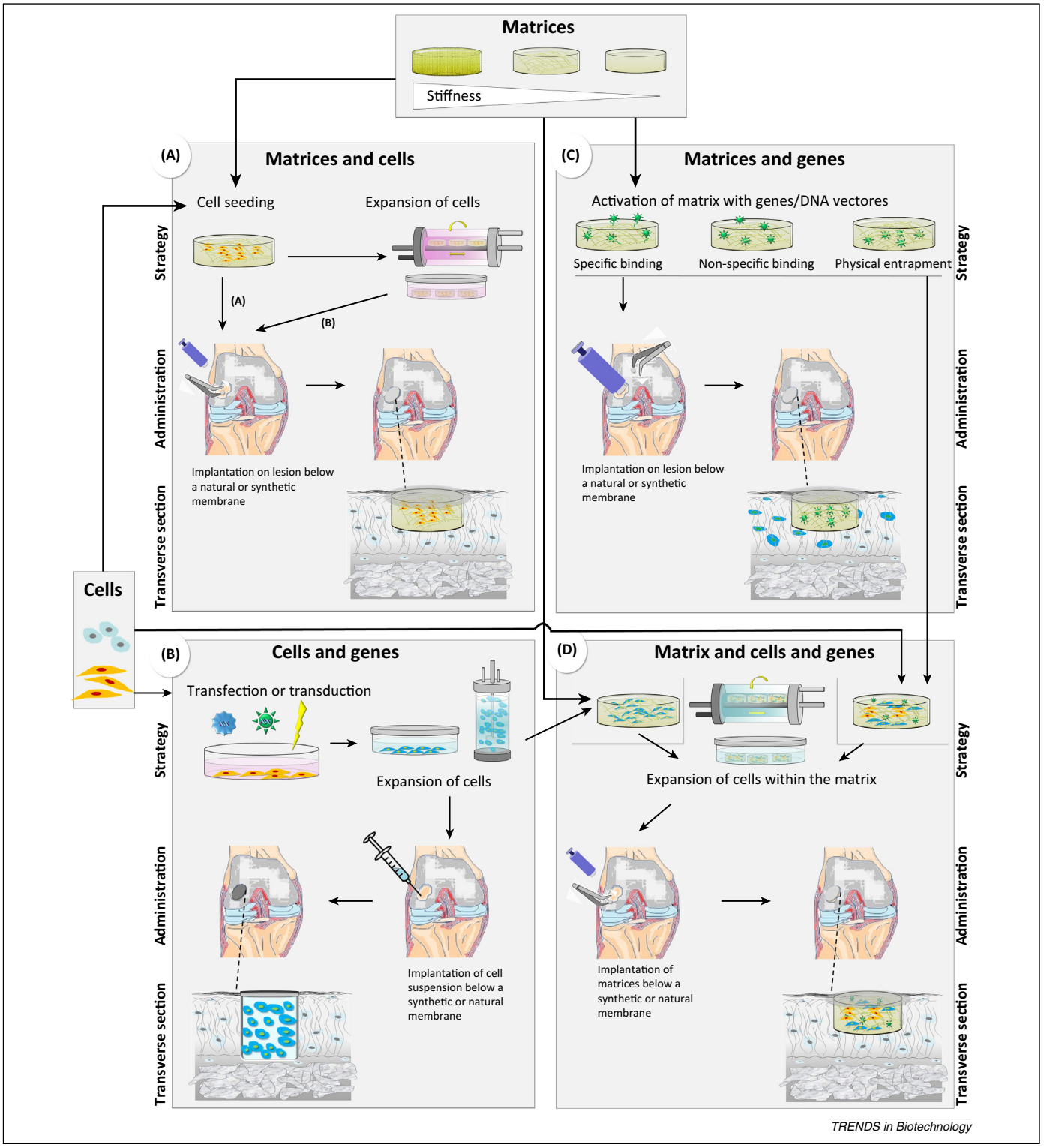

Figure 1. Combination strategies under consideration for cartilage regeneration in clinical and preclinical studies. **(A)** Matrices and cells. (a) Freshly isolated cells are mixed with a hydrogel and implanted at the lesion site. (b) Cells are seeded on a matrix and expanded under static or dynamic culture before implantation. **(B)** Cells and genes that are implanted at the lesion site below a natural or synthetic membrane. **(C)** Matrices and genes implanted after specific or non-specific binding. **(D)** Matrices and cells and genes. *In vitro* physical stimuli during cell expansion can be considered in strategies (A), (B), and (D).