

BIOREACTORS FOR CARTILAGE TISSUE ENGINEERING

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INTRODUCTION: Recent animal experiments have demonstrated that engineered cartilage tissues generated by culturing chondrocytes into 3D scaffolds provide functional templates for the orderly repair of critically sized osteochondral lesions. In order to reproducibly generate functional cartilage tissues starting from adult human cells, efforts have to be directed not only to the identification of stimulatory biochemical factors, but also to the development and use of controlled bioreactor systems, applying defined regimes of physical forces. In this work, we present some examples on the use of bioreactors for processes that are key for engineering of 3D cartilage tissues based on cells and scaffolds, namely the chondrocyte seeding into porous scaffolds, their efficient nutrition, and the physical conditioning of the developing tissues.

CHONDROCYTE SEEDING AND CULTURE UNDER PERFUSION:

In the cell seeding process, cells must be utilized with maximum efficiency to minimize the biopsy size needed and/or the extent of cell expansion, and must be dispersed uniformly throughout the scaffold volume to form the basis for uniform tissue formation. To overcome limitations associated with the most commonly employed seeding techniques, we developed a bioreactor for the automated cell seeding of three-dimensional scaffolds by continuous perfusion of a cell suspension through the scaffold pores in oscillating directions. Perfusion seeding of chondrocytes into Polyactive foams (IsoTis OrthoBiologics, NL) or Hyaff®-11 non-woven meshes (Fidia Advanced Biopolymers, IT) resulted in the highest fraction of viable cells within the foam pores, the greatest efficiency of seeding and the highest uniformity of cell distribution in comparison to the typically used static and spinner flask methods¹.

Constructs uniformly seeded by perfusion and then cultured statically for 2 weeks were highly heterogeneous in structure, consisting of a layer of cells and matrix at the periphery and an essentially void interior region. Instead, constructs cultured under prolonged perfusion were remarkably homogeneous, containing a

uniform distribution of both cells and matrix throughout the cross-section².

PHYSICAL CONDITIONING OF CARTILAGE CONSTRUCTS:

Application of dynamic compression to cell-polymer constructs could potentially improve the development of cartilaginous tissue *in vitro*. We exposed human articular chondrocytes-based cartilaginous constructs at different stages of maturation, as defined by the glycosaminoglycan (GAG) content, to intermittent compressive deformation for 3 days. Compression-induced changes in GAG synthesis and accumulation were positively correlated to the GAG content prior to loading, such that compression was stimulatory only for the most developed constructs. Therefore, under our experimental conditions, cyclic loading appears to be applicable for the enhancement of cartilaginous tissue development only in the late phases of tissue regeneration³. Our results also point out the possible use of bioreactors applying defined regimes of physical forces as a quality control tool for engineered cartilage, with the goal of defining when the tissues are sufficiently developed for immediate load bearing after implantation.

CONCLUSION: The reviewed studies indicate that bioreactors enable generation of cartilaginous tissue constructs and may contribute to understand the function of specific chemico-physical culture parameters on cartilage tissue development. In the future, bioreactors are expected to efficiently translate laboratory- to industrial-scale cartilage tissue engineering, possibly providing an economically viable approach to the automated manufacture of functional cartilage grafts for broad clinical use⁴.

REFERENCES: ¹ Wendt et al., *Biotech Bioeng* 2003; 84:205-214. ² Wendt et al., *J Biosci Bioeng* 2005; 100:489-494. ³ Demartean et al., *Biochem Biophys Res Comm* 2003; 310:580-588. ⁴ Martin et al., *Trend Biotech* 2004; 22:80-86