

BIOREACTOR-BASED TISSUE ENGINEERING STRATEGIES

Ivan Martin, Stefania Riboldi, Marcel Jakob, David Wendt

Departments of Surgery and Biomedicine, University Hospital Basel, CH

INTRODUCTION

Lately we have witnessed an increased recognition of the importance of 3D culture models to study various aspects of cell physiology and pathology, as well as to engineer implantable tissues. Bioreactor systems may provide the technical tools to address challenging scientific questions and to allow the successful translation of Tissue Engineering processes from bench to bedside.

TECHNICAL BACKGROUND

Bioreactor systems have proved to be crucial to establish and maintain 3D cell/tissue cultures, and have the potential to provide such cultures with a controlled chemico-physical environment. In particular, bioreactors may offer the following features: 1) Efficient and uniform cell seeding on 3D scaffolds, especially when relying on perfusion techniques; 2) Improved mass transfer in 3D cultures, mostly using hydrodynamic flow patterns; 3) Physical conditioning of developing constructs, since physical forces (i.e., hydrodynamic, mechanical and electrical) play a key role in tissue development and remodeling; 4) Automation of medium and gas exchange procedures, with consequent smoother variations in the concentration of key metabolites.

SCIENTIFIC CHANCE AND CHALLENGE

Bioreactor systems offer the possibility to investigate cell function, cell interactions and tissue development within controlled 3D models, which may be designed to recapitulate specific aspects of the actual *in vivo* milieu. In particular, the application of defined environmental factors will be key to gain a deep insight into the mechanobiology of tissue development, and the consequent capability to drive and actively modulate the *in vitro* generation of engineered grafts. In order to achieve these goals, critical challenges lie in the integration of bioreactor technologies with 1) model-based design (e.g., computational fluid dynamics modeling to predict actual fluid velocity and shear profiles) and 2) sensing and control techniques (e.g., online, non-invasive monitoring of the constructs functional and morphological properties, and implementation of feedback-based strategies of system control).

CLINICAL PROSPECTIVE

Even the most clinically successful products will need to demonstrate: (a) cost-effectiveness and cost-benefits over existing therapies, (b) absolute

safety for patients, manufacturers and environment, and (c) compliance to the evolving regulatory framework in terms of QC and GMP. In this context, the following bioreactor-based features and strategies will be reviewed. 1) Automating tissue culture processes: Closed and minimally operator-dependent systems for automation and control of the entire tissue manufacturing process possess great benefits in terms of safety and regulatory compliance. Such systems, despite high initial development costs, would have great potential to improve the cost-effectiveness of tissue engineering approaches and facilitate large-scale production in the long-term. 2) Streamlining conventional cell culture techniques: As an alternative to systems automating established manual culture procedures, novel concepts and techniques that streamline the conventional engineering processes (e.g., cell expansion directly in 3D scaffolds) will likely have the greatest impact on tissue manufacturing. 3) Manufacturing in centralized vs de-centralized facilities: Manufacturing at central locations allows close supervision over the entire production process, but is associated with complicated logistical issues. De-centralized production systems, located within the confines of hospitals, would simplify logistics but would involve the greatest upfront risks in terms of development time and costs. 4) “Intraoperative engineering” approaches: In spite of a paradigm shift (i.e., towards a regenerative medicine approach), *in vitro* bioreactor systems will continue to play a critical role. In fact, they will be necessary to streamline and automate biopsy processing and cell isolation/seeding, as well as to generate the knowledge of environmental factors required *in vivo* for predictable tissue development.

CONCLUSIONS

Progress made in the *in vitro* generation of 3D tissues starting from isolated cells is slowed down by the complexity of the process. By providing a comprehensive level of monitoring and control over specific environmental factors, bioreactors can provide the technological means to identify which specific chemico-physical parameter plays which function in engineering a defined tissue. At this stage, implementing the defined bioprocesses in bioreactor systems will support safe, standardized, scaleable, traceable and possibly cost-effective manufacturing processes for clinical use.