Cell-based Microfluidic Chip to Study Bone Healing Mechanisms

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Microfluidic technologies permit the replication in vitro of geometrical features essential for the homeostasis of all vascularized tissues in vivo. These in vitro models aim at reducing animal testing for drug development and at bringing a modular tool for mechanistic studies.

A functional microvasculature is critical for the homeostasis of all vascularized tissues. Accordingly, several diseases are associated with alterations in the microvasculature, like for instance in tumor angiogenesis. Furthermore, the formation of new vessels by angiogenesis is critical in the restoration of tissue function. In tissue engineering, sufficient neovascularization is thought to be a prerequisite for the integration of the implant. These conditions have been extensively studied in animal models. However, in vivo studies have several limitations, including species differences and limited possibilities for imaging and tracking cells in the living animal. They also do not permit high-throughput and multiplexing applications. The development of microfluidic models of microvasculature and the endothelial barrier could help to overcome these problems, and most importantly, would replace a significant amount of animal experimentation [1].

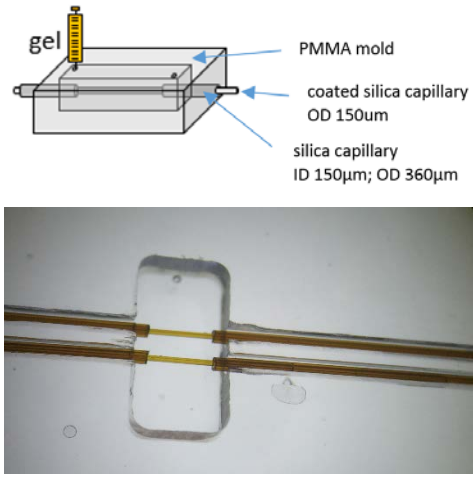

Figure 1: Drawing of the microfluidic device (top); microscopic picture of the chamber containing thin capillaries used as molds (bottom).

CSEM and the AO Research Institute in Davos (Switzerland) addressed this problem by developing a microfluidic device mimicking microvessels (diameter between 100 and 200 µm). This tool allows to study the interactions of various factors with the endothelium over the course of several days.

In order to create a perfusable microvessel, micromolding in a biocompatible hydrogel has been used, as shown in Figure 1. A cavity micro-machined in a thermoplastic layer is crossed by a microcapillary. A gel is injected and after polymerization, the capillary removed, thus leaving a cylindrical void (Figure 1, bottom and Figure 2A). The wall of the microchannel is subsequently covered by different cell types (Figure 2B). In order to bring nutrients to the cells, a perfusion system, comprising of piezo-electric pumps, reservoirs and bubble trap, was developed.

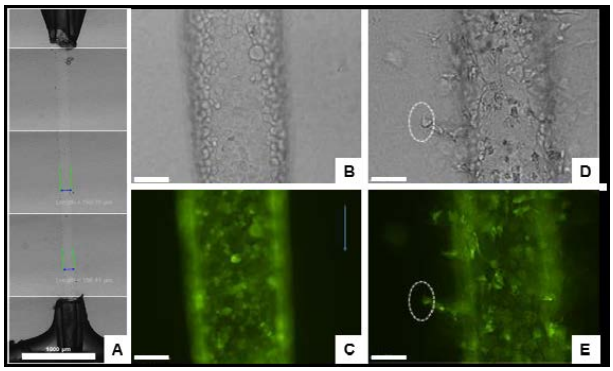

Figure 2: A) Microchannel within collagen gel. B-E. High magnification images of the microchannel seeded with GFPHUVECs after 1 h (B, C) or 28 h (D, E) of perfusion. Dotted circles indicate areas of sprouting. Scale bars 1000 µm (A); 100 µm (B-E).

This system allowed to observe endothelial cells up to 100 hours under physiological conditions, using time-lapse microscopy and fluorescence imaging.

The next iteration of this platform will bring more complexity to the in-vitro model, as well as increasing the throughput.

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• AO Research Institute, Davos, Switzerland

[1] L. Barbe, M. Alini, S. Verrier, M. Herrmann, "In vitro models to mimic the endothelial barrier", ATLA, 43 (2015) 34.