Perfusion-based three dimensional (3D) tissue engineering platform with integrated bioimpedance sensing

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Published in:
Proceedings of the 2nd IEEE EMBS Micro and Nanotechnology in Medicine Conference

Publication date:
2014

Perfusion-based three dimensional (3D) tissue engineering platform with integrated bioimpedance sensing

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***Abstract* — We present an 8-channel bioreactor array with integrated bioimpedance sensors, which enables perfusion culture of cells seeded onto porous 3D scaffolds. Results show the capability of the system for monitoring cell proliferation within the scaffolds through a culture period of 19 days.**

There is an increasing interest in the development of 3D tissue engineering systems for drug screening and organ development applications [1]. A significant challenge in this regard is the monitoring of cellular processes occurring within the scaffolds, particularly as traditional optical microscopic techniques are unsuitable for monitoring thick 3D constructs [2]. Impedance spectroscopy has been shown to be a powerful tool for non-invasively monitoring the electrical behavior of tissues and cell cultures [3]. Here we present the development of an 8-channel bioreactor array with embedded impedance sensors that enable real time monitoring of the proliferation of cells cultured on porous 3D scaffolds.

The cell culture platform consists of a polycarbonate based array of 4 x 2 bioreactors, cell culture media and waste storage vials, an 8-channel micropump and a motor (Fig. 1a). Each bioreactor unit comprises of a chamber for holding a porous scaffold, and two 400 µm diameter platinum (Pt) wires for impedance sensing (Fig. 1b, c). Human hepatoblastoma (HepG2) were seeded onto porous polymer scaffolds (6 mm diameter and 5 mm high) with a seeding density of 2 x 10^6 cells/scaffold. The cell laden scaffolds were loaded into the bioreactors and culture media was perfused through them at a flow rate of 5 µL/min (corresponding to a media exchange in the bioreactor approximately every 18 minutes). Impedance measurements were carried out by applying a sinusoidal perturbation of 10 mV (rms) across the Pt electrodes in the frequency range spanning 10 Hz to 1 MHz. At the end of the cell culture period, the quantity of cells within the bioreactors was established by measuring the double stranded DNA content using the Quant-iT™ PicoGreen® dsDNA Reagent (P7581, Life Technologies). Fig. 2 [a] shows the measured impedance magnitude |Z| (at a frequency of 10 kHz) over the 19 day culture period for four bioreactors. There was an observed overall drop in impedance during the first three days of the experiment, which may correspond to the loss of cells that have not attached to the scaffold (following seeding) due to perfusion of media. This was followed by a net increase in measured impedance over time in all cases.

*Research financially supported by the EU-funded project NanoBio4Trans (grant no. 304842)

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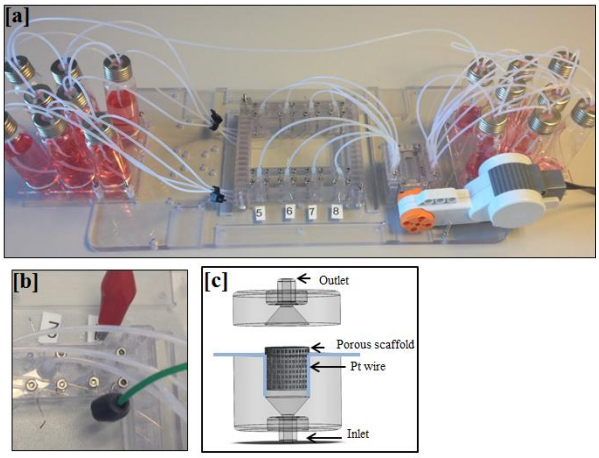

Figure 1. [a] Cell culture platform with array of 4 x 2 perfusable bioreactors, [b] magnified view of bioreactor with integrated Pt based bioimpedance sensing electrodes, [c] Schematic of single bioreactor unit.

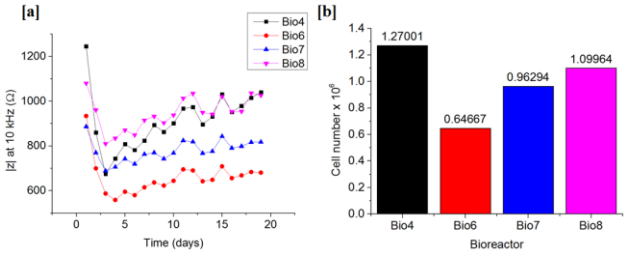

Figure 2. [a] |Z| at 10 kHz vs. time over a cell culture period of 19 days, [b] Cell number in each bioreactor at the end of the 19 day culture period.

Fig. 2[b] shows the total cell count in each bioreactor at the end of the culture period, which demonstrates the correlation between cell density and measured impedance. Further investigations are currently underway to characterize the distribution of cells within the scaffold in order to assess its impact on the measured impedance.

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