Scientific Paper:

TISSUE ENGINEERING: Part C, Volume 24, Number 10 (2018)

A Perfusion Bioreactor System for Cell Seeding and Oxygen-Controlled Cultivation of Three-Dimensional Cell Cultures

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Abstract:

Bioreactor systems facilitate three-dimensional (3D) cell culture by coping with limitations of static cultivation techniques. To allow for the investigation of proper cultivation conditions and the reproducible generation of tissue-engineered grafts, a bioreactor system, which comprises the control of crucial cultivation parameters in independent-operating parallel bioreactors, is beneficial. Furthermore, the use of a bioreactor as an automated cell seeding too enables even cell distributions on stable scaffolds. In this study, we developed a perfusion microbioreactor system, which enables the cultivation of 3D cell cultures in an oxygen-controlled environment in up to four independent operating bioreactors. Therefore, perfusion microbioreactors were designed with the help of computer-aided design, and manufactured using the 3D printing technologies stereolithography and fused deposition modeling. A uniform flow distribution in the microbioreactor was shown using a computational fluid dynamics model. For oxygen measurements, microsensors were integrated in the bioreactors to measure the oxygen concentration (OC) in the geometric center of the 3D cell cultures. To control the OC in each bioreactor independently, an automated feedback loop was developed, which adjusts the perfusion velocity according to the oxygen sensor signal. Furthermore, an automated cell seeding protocol was implemented to facilitate the even distribution of cells within a stable scaffold in a reproducible way. As proof of concept, the human mesenchymal stem cell line SCP-1 was seeded on bovine cancellous bone matrix of 1 cm^3 and cultivated in the developed microbioreactor system at different oxygen levels. The oxygen control was capable to maintain preset oxygen levels ± 0.5 % over a cultivation period of several days. Using the automated cell seeding procedure resulted in evenly distributed cells within a stable scaffold. In summary, the developed microbioreactor system enables the cultivation of 3D cell cultures in an automated and thus reproducible way by providing up to four independently operating, oxygen-controlled bioreactors. In combination with the automated cell seeding procedure, the bioreactor system opens up new possibilities to conduct more reproducible experiments to investigate optimal cultivation parameters and to generate tissue-engineering grafts in an oxygen-controlled environment.

Keywords: oxygen measurement, feedback control, cell seeding, perfusion microbioreactor, 3D cell culture