3D printed microfluidic systems for cell culture and biological applications

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Microfluidics and the development of “lab-on-a-chip” (LOC) systems offer a great potential for a wide range of applications in medical engineering, biotechnology, biology and chemistry. Due to their capability to enable precise and rapid manipulation of cells and other biological samples, the interest in micro-structured systems has increased in recent years. In regard to biological applications, systems miniaturization can provide new strategies for testing the dynamic cell response to various external influences. In addition, LOC systems allow for the establishment of continuous and reproducible experimental conditions and therefore they can maintain a native, physiologically favorable cell environment.

The small required sample volumes, low reagent consumption and the highly controlled and reproducible environment, benefit various biological applications from nucleic acid and protein analysis to drug development and drug delivery. Additionally, numerous microfluidic systems for cell cultivation and cell manipulation have been reported, demonstrating capabilities, which would be far more complex to achieve, using traditional techniques. An example of a microfluidic system that can be implemented in a cell culture process is shown in figure 1. Despite the various applications demonstrated, the commercial use of microfluidics is still extremely limited. One reason for this lack of commercialization is the complex and time-consuming fabrication of the devices.

In recent years, three-dimensional (3D) printing has attracted growing scientific attention. Remarkable technical advances make it possible for high-definition (HD) structures to be printed on a scale of only few micrometers. These developments can also be brought to bear in microsystem technology, and are increasingly exploited for 3D printing of microfluidic prototypes and single-use systems. Innovative HD 3D printing technology is increasingly used for the development of LOC prototypes for cell culture processes. A major advantage of 3D printed microsystems compared to traditional microfabrication methods is that desired prototypes can be printed within few hours. The 3D design and flow simulations of the LOC device can easily be performed using suitable software. Therefore, modifications needed in order to optimize the microfluidic system can be rapidly implemented and tested. An example of the 3D printing process for a micromixer is shown in figure 2.

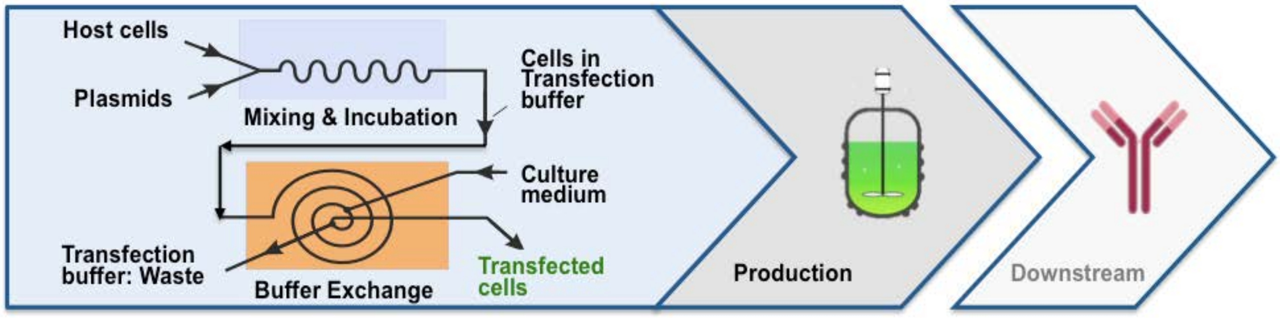

Fig. 1: Flexible production of biopharmaceuticals using a LOC system:

The integrated microfluidic system allows for a flexible production of recombinant proteins. The demonstrated system consists of several functional, integrated microfluidic units: First, there is an efficient mixing and incubation of host cells with plasmid (including the gene of interest) and transfection reagent. This part allows for a continuous transfection of mammalian suspension cells. Second, a spiral separator separates the transfected cells from their transfection medium while the cells are transferred to fresh cultivation medium at the same time. Finally, the cell suspension flows to a bioreactor for further cultivation and protein / antibody production.

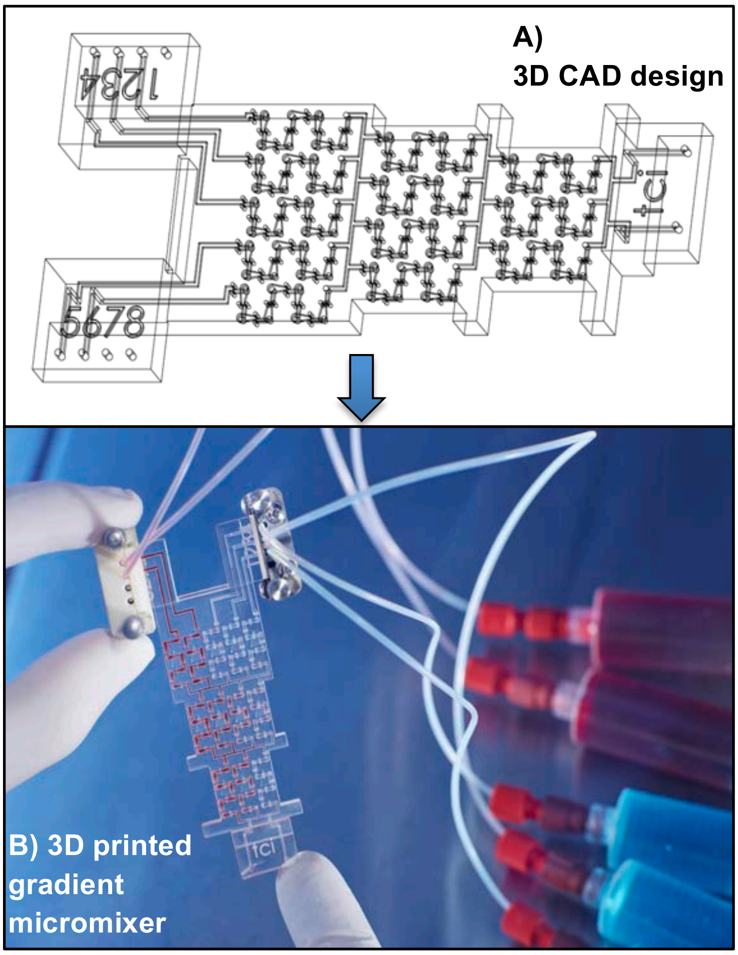

Fig. 2: From 3D design to 3D printing: A) 3D-CAD (Computer-aided design) of a tree-shaped gradient micromixer. B) The 3D printed tree-shape gradient micromixer that allows for the rapid mixing of solutions in order to achieve a defined concentration gradient at the outlets of the device.