THE FUTURE OF CLINICAL TRIALS – ORGAN ON CHIP TECHNOLOGY

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Contents

Introduction –

Organ-on-Chip (OOC) refers to a new class of biomedical research which involves the development of microfluidic devices lined with organic human tissue [1]. These devices are able to mimic blood flow, the mechanical microenvironment within biological structures of organs, and the physical interfaces in-between living tissue [2]. This allows the devices to accurately model a range of human organs [3], and has the potential to be used for non-invasive monitoring of cell health during the testing of pharmaceutical drugs molecules, toxins and bacteria. Fabrication techniques, lung on chip, limitations and future developments are discussed in this review.

Context –

The primary feature of OOC systems are their ability to precisely mimic the biomechanical and biochemical micro environments of human tissue and internal interactions with drug molecules [3]. These OOC models are exposed to inputs; drug molecules, toxins and bacteria. Outputs such a chemical concentration changes within fluids and cellular reactions of the organic human tissue are monitored [2]. This demonstrates a highly effective tool for clinical testing and provides an opportunity to diverge from conventional animal testing and the associated ethical concerns [1]. OOC systems also have the potential to provide a higher degree of clinical test accuracy due to biological differences in the human and animal micro environment [1][2][3] and has the potential to significantly reduce the cost of clinical trials by eliminating the cost incurred through animal procurement and management [3][4].

Current State of the Technology –

Fabrication of microfluidic devices for OOC systems inherently relies on micro engineering techniques [4]. The recent development of or organ on chip technology can largely be attributed to the technological advancements made within the microelectronics fabrication industry [4] [5].

The current dominant technique for fabrication of microfluidic devices "PDMS Soft-lithography" [6], is a rapid prototyping technique adapted from the microelectronics manufacturing process "lithography" [6], this process is well documented within "The application of photolithography to the fabrication of microcircuits" by J T M Stevenson and A M Gundlach [7] . PDSM soft lithography includes an additional step (see step e & f below), whereby a flexible PDMS polymer is poured over a master template and set. The removal of the solid PDMS polymer results in imprinted 3D microstructure's within the PDMS polymer [8].

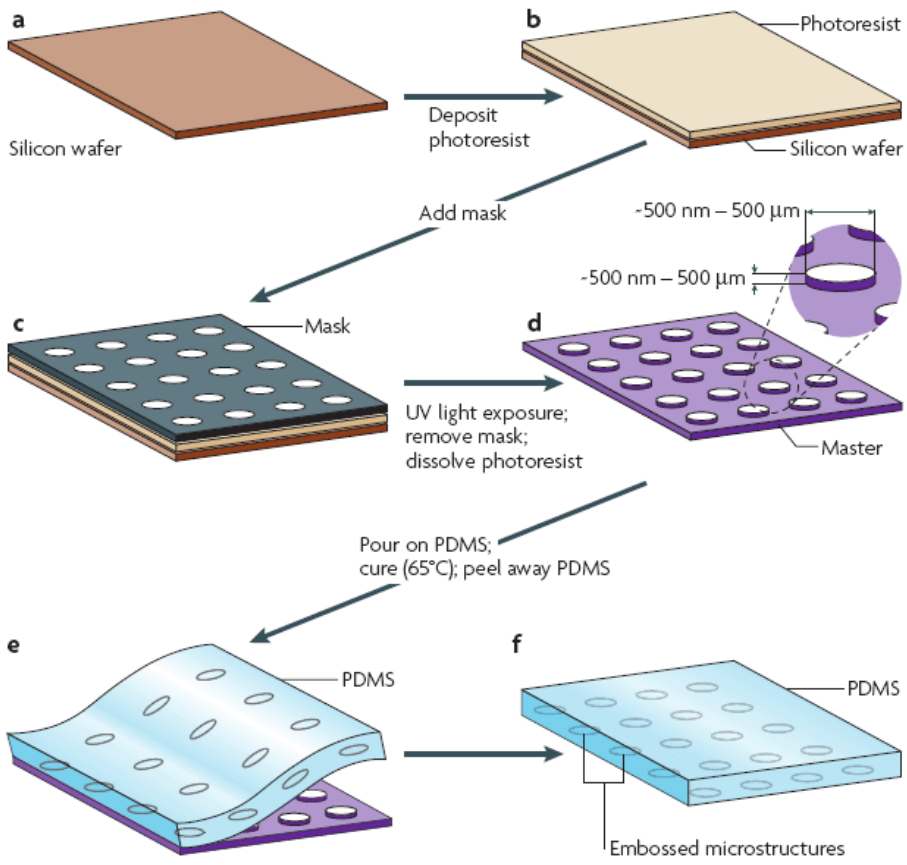

Figure 1: "Fabrication of a PDMS layer incorporating microstructures. Drawings (a) – (d) correspond to the fabrication of a rigid master via photolithography. Drawings (e) and (f) can be considered as part of the soft lithography process" [6] [8]

The PDMS Soft-lithography process is used to create microfluidic channels within the flexible polymers. These channels are then lined with living human cell cultures that are specific to the organ to be mimicked [1] [8]. A combination of fluidic flow and mechanical deformation specific to the organ of interest can mimicked by pumping fluids or creating pressure differentials within certain channels [4].

The following demonstrates the typical mechanical functions OOC systems using the “Lung-on-Chip model” developed by the University of Harvard’s Wyss Institute as an example. [1]

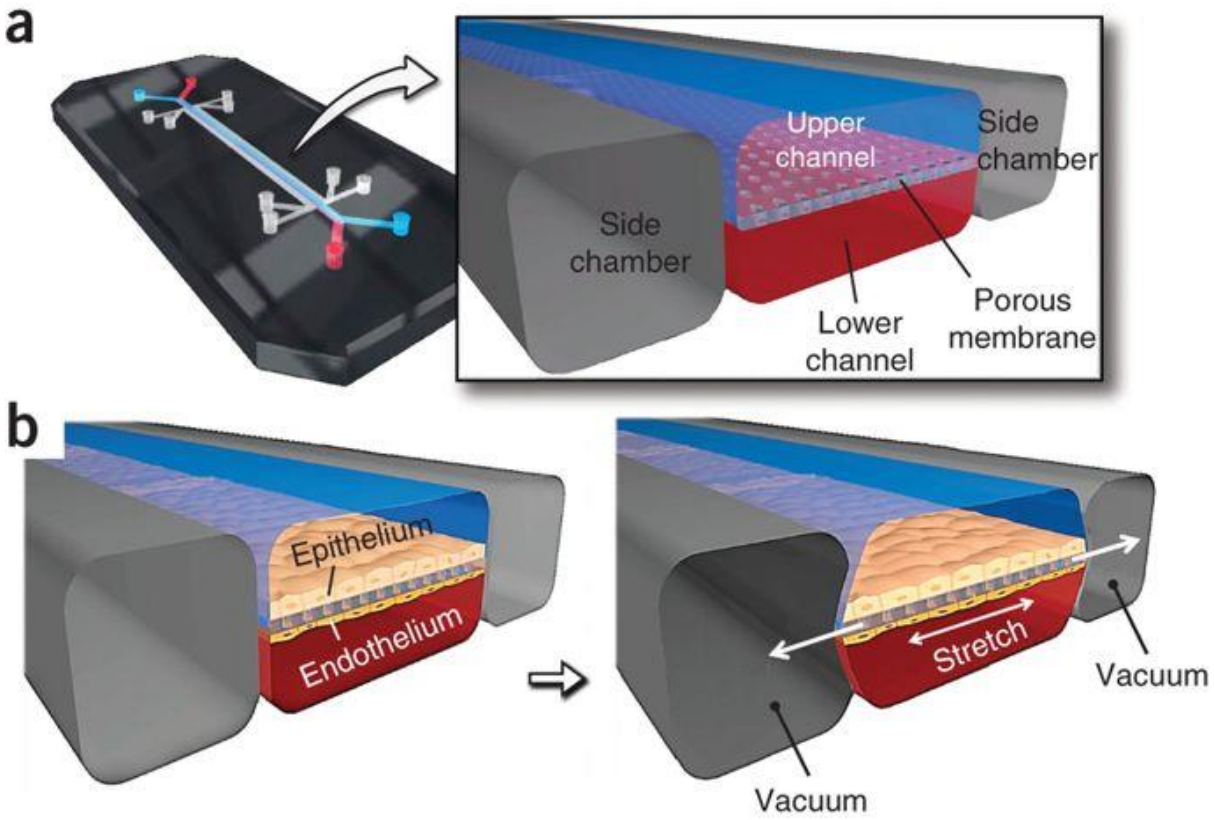

Figure 2: Lung-on-chip microsystem [1][4]

(A) The “lung-on-chip” model contains of a three micro fluidic channels [4]. The central channel is multi-layered and comprised of an upper air channel (blue) and lower blood channel (red), separated with a micro fabricated porous membrane. The side chambers (grey) are hollow.

(B) The porous membrane is lined with two types of cultured human cells; Epithelium (lung cells) and Endothelium (capillary cells) [1]. The blue channel has air pumped through it, and the red channel has blood pumped through it. The application of a vacuum on the hollow chambers stretches the cell lined membrane and mimics the physiological breathing mechanism of the lung [1] [4].

For the modelling of respiratory infections or clinical testing of drug molecules, bacteria or drug molecules would be introduced to the air channel [1] [4]. The human cell behaviour within the blood channel and porous membrane is then monitored via a fluorescent microscope. This provides an understanding of the effect that prolonged exposure of bacteria or drug molecules has on the reactionary mechanisms of the human tissue or cells.

Potential and future Developments of Organ on Chip Technology –

3D bio-Printing technology has significant potential to aid to the development of OOC systems [6]. PDMS Soft-lithography as described previously is a multifaceted process which requires semiconductor lithography fabrication systems, and specialist facilities and operators [6]. 3D bio-printing has the benefit of reducing the fabrication process to a single step [9], while retaining the accuracy of PDMS soft lithography [6]. Among other considerable advantages, 3D bio printing has the capability print a range of bio materials within a single fabrication process. This improves the ability to create highly accurate scaffolds for cell culture growth [6] [11] [9], diversifying the range human microenvironments that can be accurately replicated in the organ-on-chip model.

The inclusion of electronic sensors within the OOC systems could provide significant improvements to the development and clinical efficacy of the technology. Continual monitoring of the organ-on-chip model for responses in the living tissue over a large period of time presents its own set of challenges since monitoring is typically achieved through the use of continual fluorescence microscopy [5]. In cases where drug molecules delayed responses within cell tissue [10] [11] [10] continual monitoring can prove unpractical. In order to overcome these challenges developments have been made to include commercially available sensors into the OOC system [11] [12].

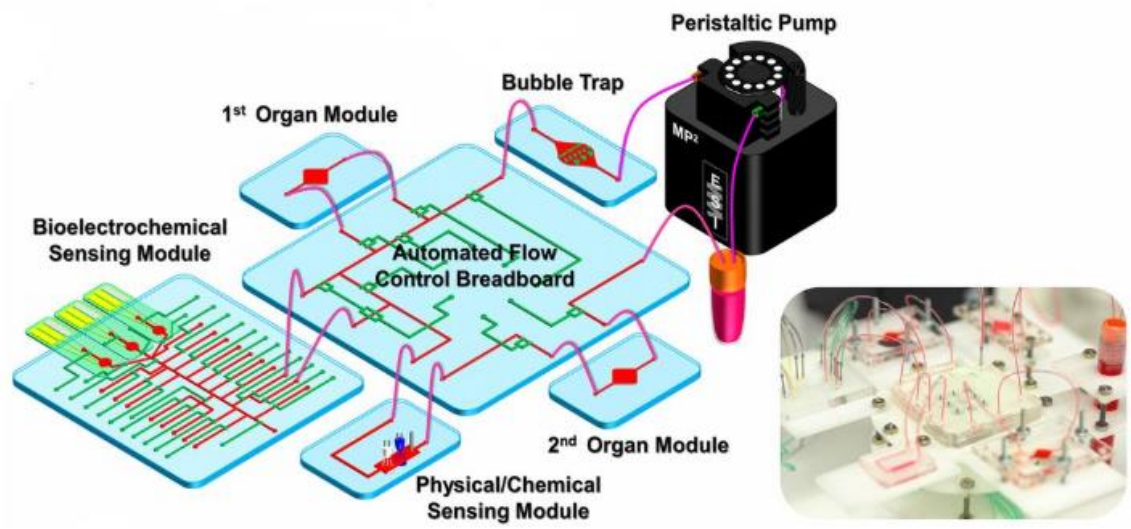

Figure 3: *Integrated automated multi organ-on-a-chip and sensing platform.* [12]

This platform allows for automated continual monitoring, which could easily be automated and provide real time measurement of a wide range of cellular parameters, such as; PH, temperature levels [10] [11][12], thus providing a deeper understanding cellular response when exposed drug molecules.

Limitations

While the OOC system has seen significant development in recent years and can be used as a powerful tool to aid drug discovery and development, it does have limitations in its current state.

While 3D microenvironments mimicked within the OOC system do represent many of the cellular functions present in real tissue, many functions are yet to be accurately reproduced [13]. Using the liver-on-chip model system as an example, sinusoidal liver tissue is responsible for many cellular interactions within the liver, such as disease development, and detection of poisonous substances [13]. However, sinusoidal tissue is yet to be accurately reproduced in the liver-on chip model. This significantly limits the capability of the liver-on-chip system since it cannot simulate pathogenesis or reactions to toxins [13].

The current dominant technique of PDMS soft-Lithography also present significant challenges in OOC technology. [4] Polydimethylsiloxane (PDSMS) used to create microfluidic channels in OOC devices has a poor chemical resistance to solvents used within drug discovery and development processes. This poor chemical resistance [4] limits the type of drug molecules that could be tested using the OOC system and effects accuracy of results when testing some drug molecules due to absorption of hydrophobic molecules [4]. This demonstrates a need to develop a chemically un-reactive, malleable material that could be used to for OOC fabrication without imposing limitations on the functionality.

Conclusion

The OOC model clearly demonstrates a significant advance in the scientific ability to simulate the specific cellular functions within the human body, and their reaction to specific drug molecules bacteria, and toxins. While the technology is still in its infancy the significant improvements it will bring to pharmaceutical and medical development is clearly displayed through the rapid rate of which this technology has been developed [14]. Although the OOC model does have a range of clearly documented limitations, there is a vast network of active engineers, physicists, chemists and medical specialists whom all propose solutions to these limitations. As a developing technology, the organ-on-chip model is an exceptional example of the power that interdisciplinary collaboration has when trying to achieve a common goal within the field of medical technology.

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