LAB ON A CHIP PERFUSION DEVICE FOR CONSTRUCTING MICRO-PHYSIOLOGICAL IN VITRO MODEL OF HUMAN ORGANS

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Micro-physiological *in vitro* models providing *in vivo* like environment has abundant prospects in the field of drug discovery and monitoring the physiological events. These models are currently achieved in setups like dual compartment cell culture Transwell system in which cells are grown in an insert with a porous membrane. Such *in vitro* tools are static in nature and therefore cannot simulate fully the *in vivo* conditions inside body [1]. Using these techniques needs a large amount of cells, reagents and culture media, which makes this a rather expensive approach. These models are also limited with number of simulated parameters, and are dedicated to a particular application [2-3]. In our previous work [4], we have tested an intestinal model using porous silicon membrane with pores of well controlled dimensions.

In this study, we are developing a microfluidic-based lab-on-chip platform for studying the interaction of various types of cells by co-culturing them and to use this platform for *in vitro* modeling of human organs. Here, the processes used in typical cell culture experiments are incorporated in an independent microfluidic platform. We report the characterization and optimization of device designs accomplished by means of in-depth FEA simulations (Fig. 1). The chip is made from silicon substrate, which allows us to create features with well controlled dimensions and the critical structures are realized by Deep reactive-ion etching (DRIE) process. The silicon chip itself is 15 mm wide and 40 mm long, capped with glass by means of anodic bonding which provides a leak proof fluidic system and the fluidic channels are accessed through a polymethyl methacrylate (PMMA) jig (Fig. 3). We have developed different chip designs suitable for diverse applications. The major component of the microfluidic device is a perfusion-based microflouidic structure (Fig. 2) which allows the communication between different cell types as well as facilitates the fluid flow. The cell co-culture (Fig. 4b) is achieved by growing them in discrete chambers separated by porous barriers which forms the perfusion structure. The perfusion channels provide opening ranging from 4 to 30 μm^2 optimized based on the function of each chamber.

This platform provides dynamic environment by precisely controlling the flow rate, spatiotemporal gradients, mechanical stress by fluid flow etc. which enable us to mimic the tissue structure and functions with better physiological relevance. This Organ-on-a-chip design can offer several cell culture chambers with either identical or different cellular structures to study the role of each cell type as well as to compare the cell response to various chemical exposures in parallel experiments.

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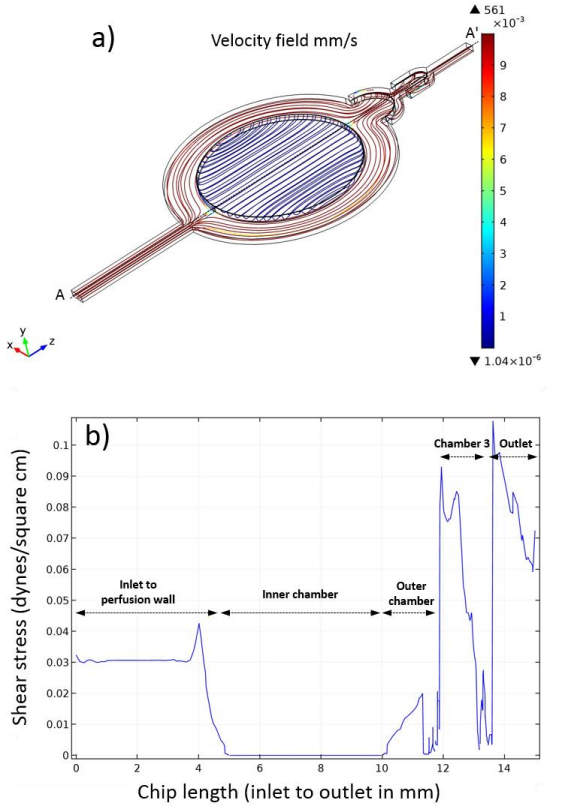

Fig.1 Simulation results of silicon microfluidic chip (Design 1) a) Velocity streamlines of fluid when flow rate of 10 nl/sec is applied at the inlet. It can be observed evidently that the liquid perfuse through the narrow channel structures of each chamber. b) Shear stress experienced at 10 um above chamber floor across the chip length, along the AA' line indicated in (a). This is an important parameter to be optimized to mimic the dynamic condition inside the body such as shear stress experienced by the cells due to fluid flow.

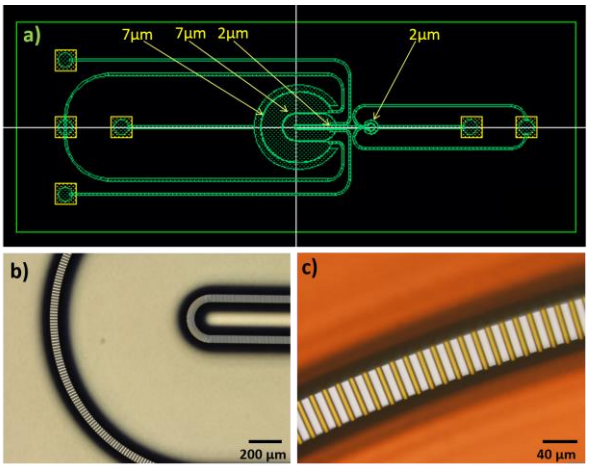

Fig. 2 a) Layout of a microfluidic silicon chip 2) with different chambers for confining different types of cells. Each chamber is surrounded by perfusion channel of different pore size. b) Microscopic image showing three different chambers separated by perfusion channels c) Image demonstrating fluid in adjacent chambers connected through perfusion channels.

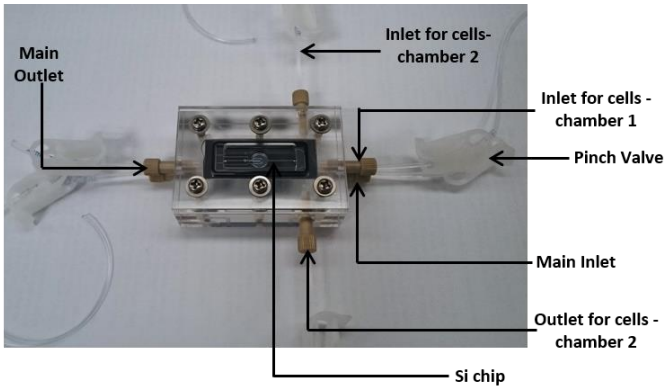

Fig. 3 Photograph of the experimental setup. The sample was driven by precise syringe pumps.

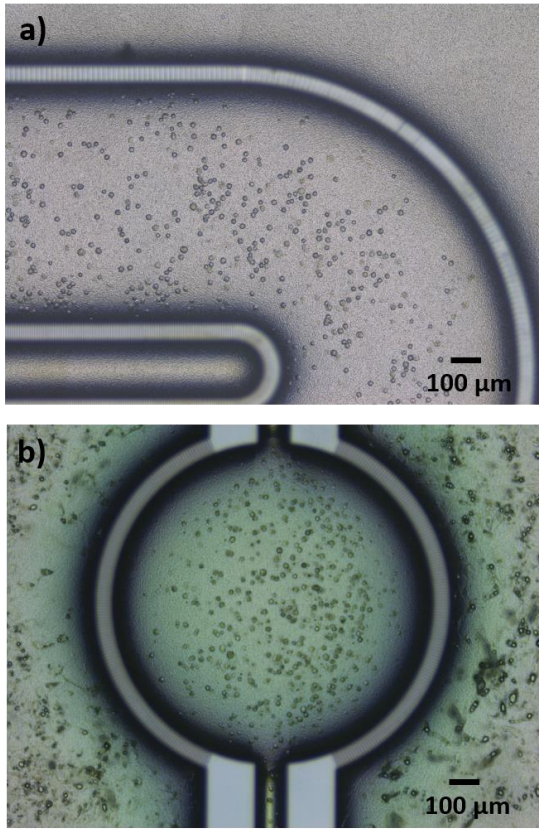

Fig. 4 Image showing Caco-2 (cell line widely used for modelling gastrointestinal barrier) cells confined in a chamber for culturing. b) A co-culture setup where Immune cells (U-937) are cultured in inner chamber and Adipocytes in outer chamber to study the adipocyte-immune cell interaction and immuno-metabolic modulatory properties in human obesity-associated in type II diabetes.