Design of a Microfluidic Device to Measure the Deformability of Cancer Cells

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Abstract and Background:

Metastasis is defined as a "tumor growth or deposit that has spread via lymph or blood to a body area remote from the primary tumor in a cancer patient" [1]. To spread in this manner, cancer cells must deform and pass through dense tissues or blood vessels with constrictions as small as a few microns. Understanding how these metastatic cells deform may give researchers valuable information to diagnose or treat cancerous patients.

The project goal was to create a polydimethylsiloxane (PDMS) microfluidic device that enables the perfusion of cancer cells through narrow constrictions while imaging the cells on a microscope. The well-defined constrictions would force the cell to deform its usually stiff and large nucleus and permit its mechanical characterization. We expect metastatic cells to be more deformable and to transit through the constrictions faster than non-metastatic cells.

The device design was generated using AutoCAD software and transferred to a wafer by photolithography with spin-coated SU-8 photoresist. The wafer was then used as a mold for the final PDMS channels. The cells entered the device through an inlet and were perfused through multiple 5 × 10 μm constrictions. The efficiency of the device is currently being evaluated using images acquired by high-speed video microscopy.

Microfluidic devices for studying nuclear mechanics are not new. However, previous perfusion devices presented problems that greatly impeded their success. In these predecessors, clustering of cells, accumulation of debris and other large particles frequently clogged the main channels of the microfluidic device containing the constrictions.

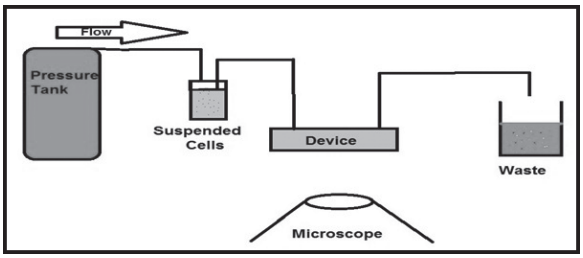

Figure 1: Schematic of perfusion experiments. A gas cylinder pressurizes the air in a tube with the cell suspension, pushing cells through the device at a constant pressure. The device is imaged using a microscope equipped with a high speed camera.

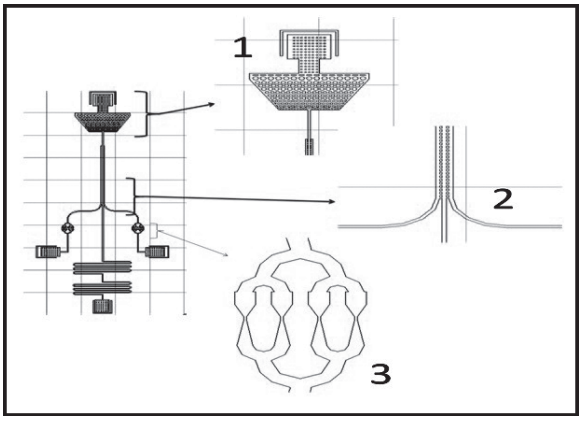

Figure 2: Innovations to the perfusion device design. Seventeen different devices were created with variations in cross-flow filter length, size of constrictions or shape of pillars in cross-flow channel.

Methods:

Devices were designed using AutoCAD software. These patterns were then transferred to a silicon wafer spin coated with SU-8 photoresist using photolithography. The PDMS was poured over the wafer, cured, peeled off, and bound to a glass slide to create the actual experimental device [2]. Perfusion experiments were performed to test the functionality of the devices. Cells in suspension were pushed through the device by a constant pressure of 10 psi. A schematic of the perfusion experiment is shown in Figure 1.

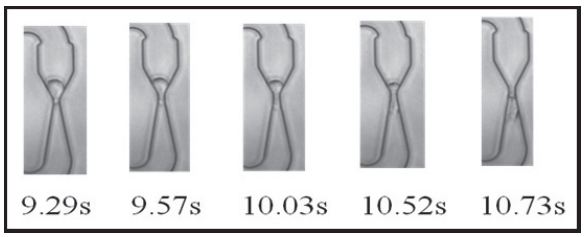

Figure 3: Cell passing through a single constriction in the perfusion device. Below each frame is the time stamp from the video, in seconds. As seen in this example, most cells pass through the 5 x 10 µm constrictions very quickly, making the high speed imaging a necessity for data analysis.

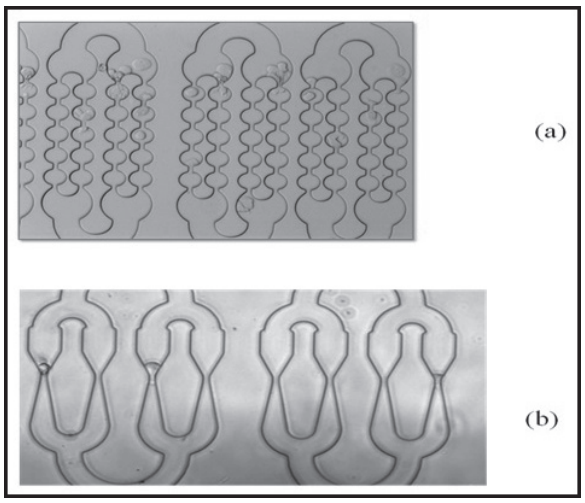

Figure 4: Device comparison. (a) The previous perfusion device, where larger particles and accumulation of cells block the main channels. (b) The new device, which only shows clogging in the far left channel, but is otherwise better suited for perfusion experiments.

Results:

Our new device design (Figure 2) features; (1) an improved coarse filter to hold back debris and larger cells, (2) a cross-flow filter [3] whose purpose is to sort the cells and keep them in a single file to prevent clustering of multiple cells, and (3) redesigned funnel shaped constrictions, through which the cells must deform. A wafer with 17 different variations of this new device was made. The devices varied in small details such as length and width of the cross-flow filter, round or square pillars, and the type of constrictions (single funnel, multiple funnels, or bubbles).

Using the same experimental setup as in previous experiments, we observed significantly reduced clogging of the revised microfluidic device. While devices based on the previous design typically became clogged within a minute or two of the start of the experiment, the new devices performed for periods of 30 to 60 minutes without the constriction channels becoming blocked, allowing for more time to collect experimental data.

After perfusion experiments, an average of 53% of cells were routed into the side constriction channels. Out of these channels, less than 20% of the channels became clogged at any given time. This is a significant improvement over previous designs that exhibited clogging in more than 50% of the channels. Based on preliminary observations, the different variations in length or shape of cross-flow filter had no discernible effect on cell sorting or prevention of blocked channels.

Conclusions:

The new device exhibits reduced clogging and more sustained throughput during the perfusion experiments. Future work will analyze the deformation of the cell nucleus when passing through the constrictions of these perfusion devices in metastatic and non-metastatic cancer cells.

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References:

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