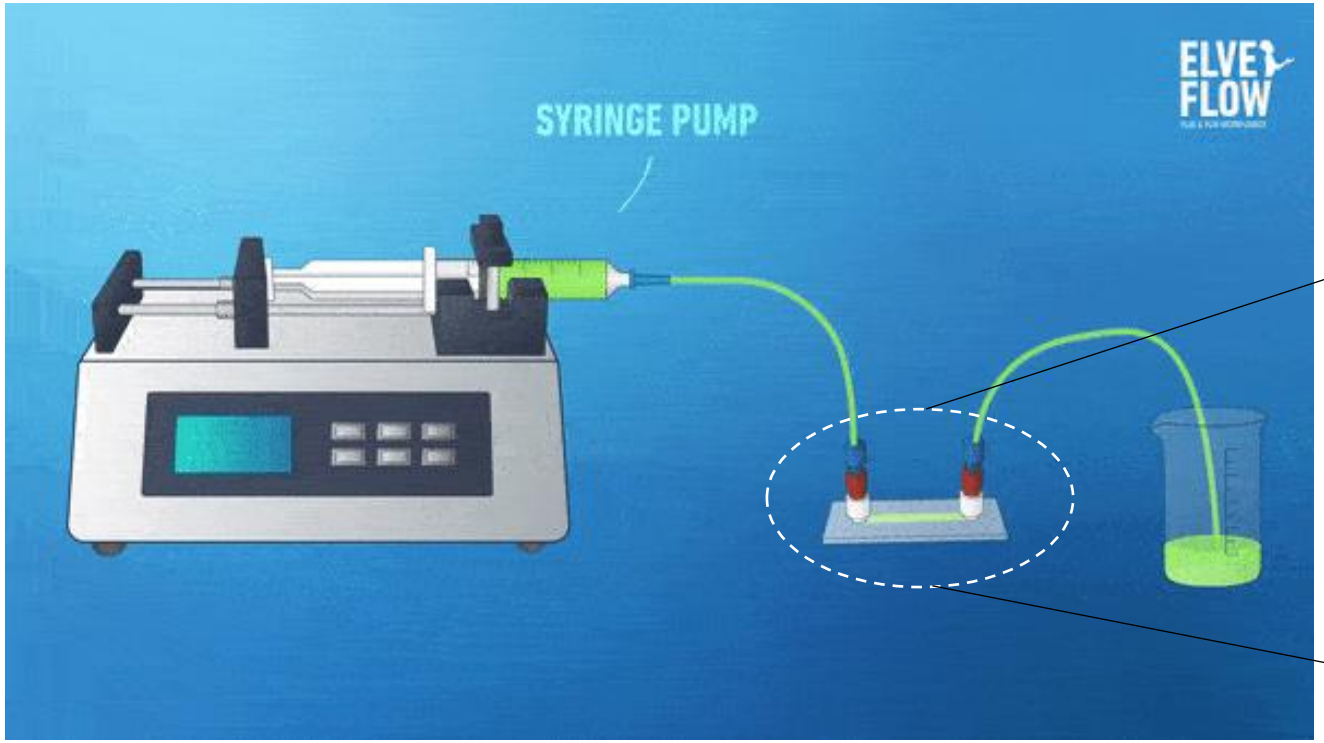
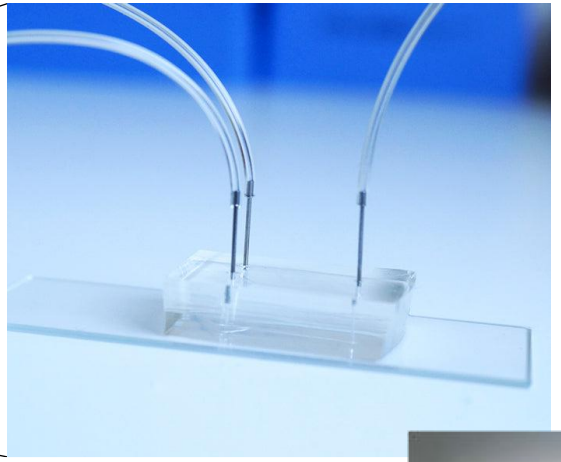
# BBL 737- MICROFABRICATION

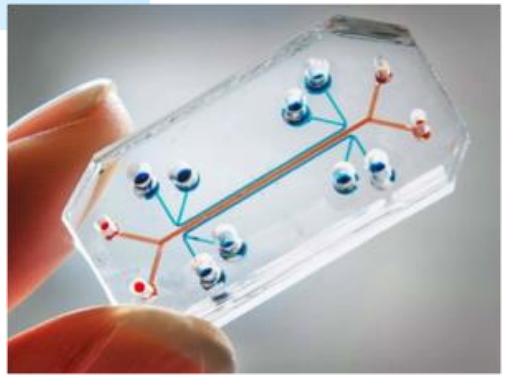
# Contents

- Microfluidics
- Microfabrication technique to fabricate microfluidic devices
- Scope of microfluidic experiments in biological system
- Governing equations for microfluidic flows

# Microfluidic Device





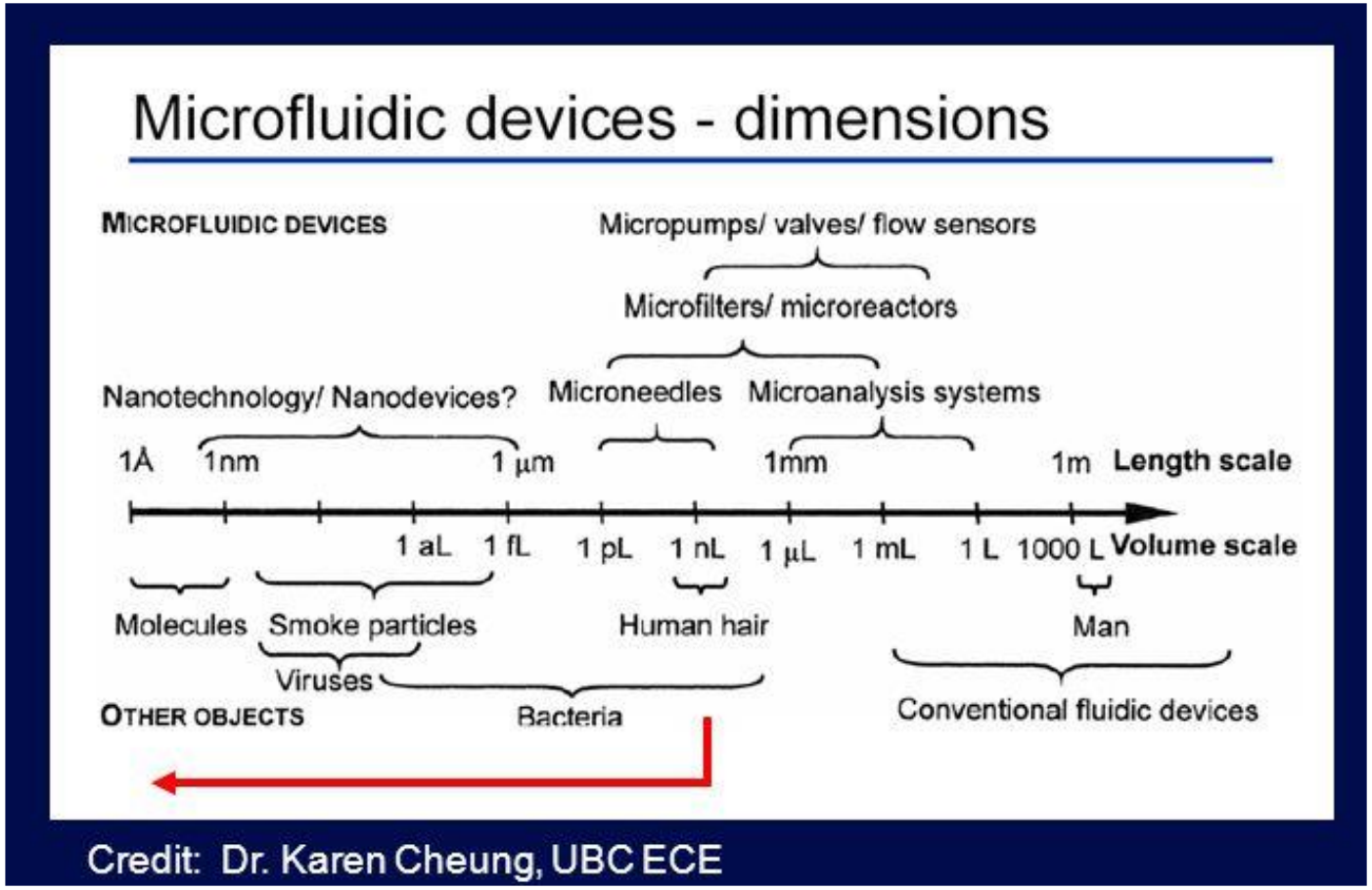
- Macromolecular analysis (DNA, Proteins, etc.)
- Disease detection and diagnostic purposes
- Drug testing/adminitration
- Cell manipulation

# Microfluidics

- Study of fluid flow with characteristic length scale of the order of Microns

- Processes and devices that deal with volume of fluid in the ranges between pico-liters to nano-liters

# Microfluidics



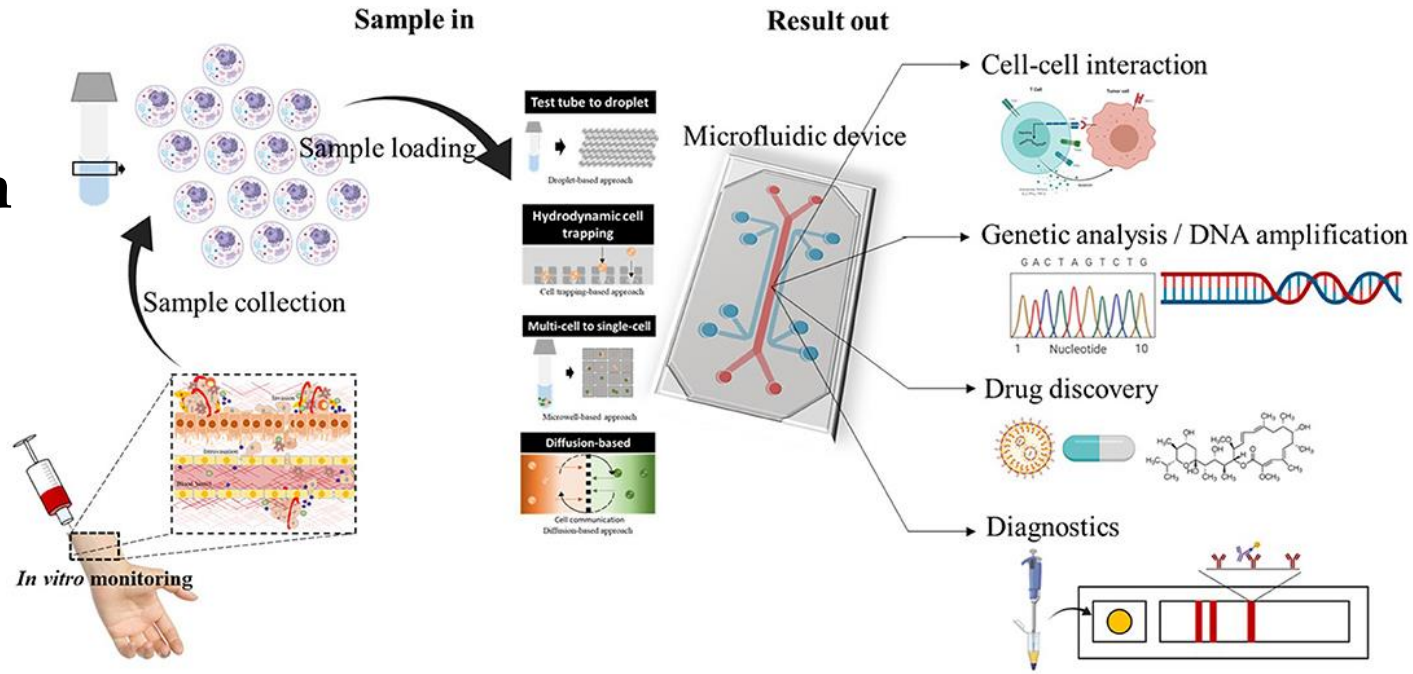
# Why miniaturization?

- Minimize material consumption and sample
- Reduction of power budget
- Faster analysis (scaling)
- Exploitation of new effects

- Required when application demands handling of very small volumes (drug administration)
- Cost/performance advantages
- Improved reproducibility, improved accuracy and reliability

# Implications in biological systems

- Fundamental understanding of biophysical processes
- Manipulation and analysis of biological macromolecules (DNA/RNA), proteins, cell, etc.
- Biomedical diagnostics
- Drug delivery/Blood extraction



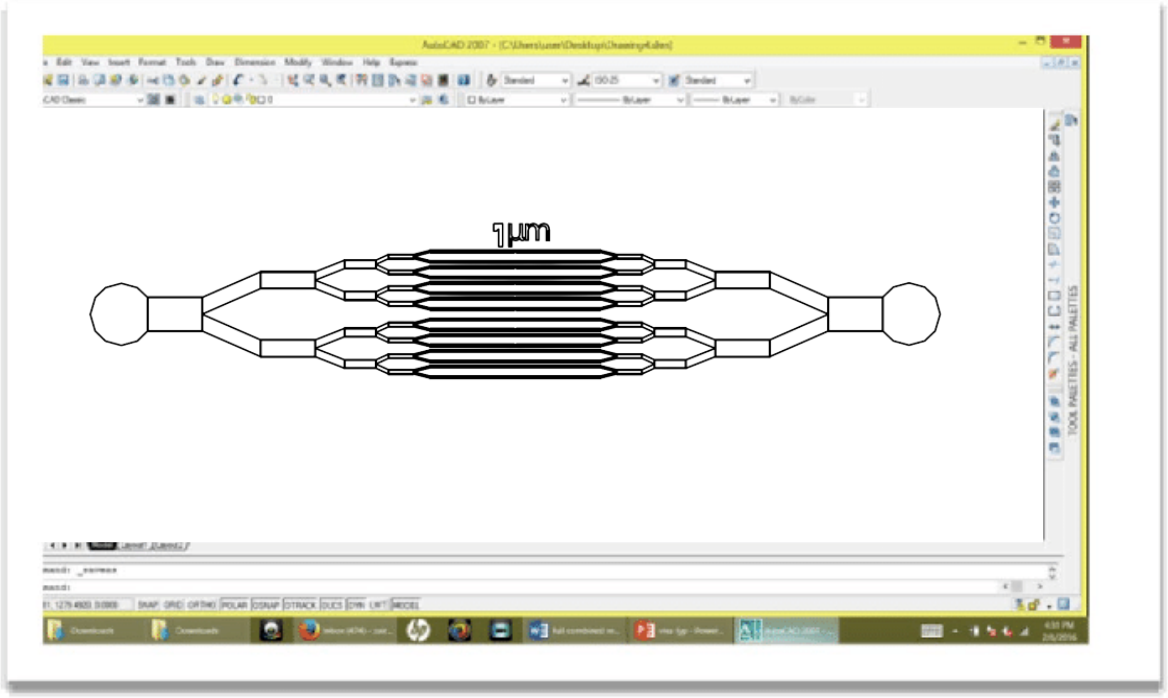
# Microfabrication or Photolithography Technique

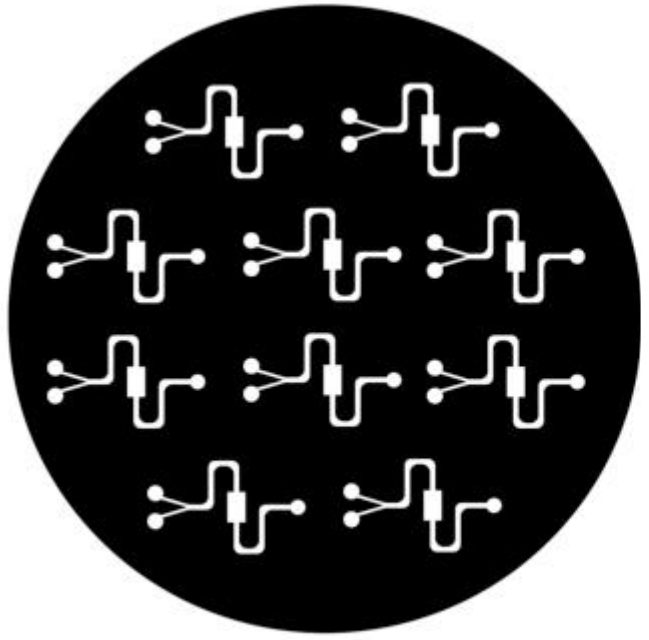
1. Circuit design and mask printing
2. Precleaning and dehydration of wafer
3. Wafer coating with photoresist (film deposition)
4. Pre-exposure soft bake
5. Mask-alignment
6. Post-exposure soft bake
7. Development (Wet-etching)
8. Hard bake
9. Soft-lithography
10. Inspection of wafer
11. Plasma bonding

# Fabrication of Microfluidic Device

## 1. Circuit design and Printing on Mask

Softwares to design the circuit – AutoCAD/FreeCAD, Clevin, DraftSight



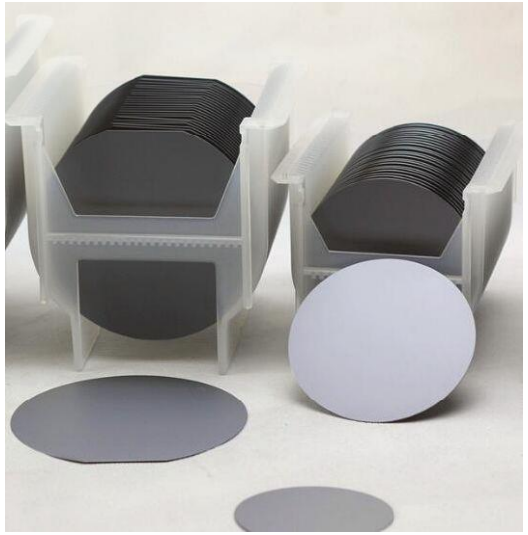



Quartz-mask (photo resistant) with embedded patterns

# Fabrication of Microfluidic Device

## 2. Precleaning and dehydration of silicon-wafer (2”, 3”, 5”…)

Thin slice of wafer serve as a substrate



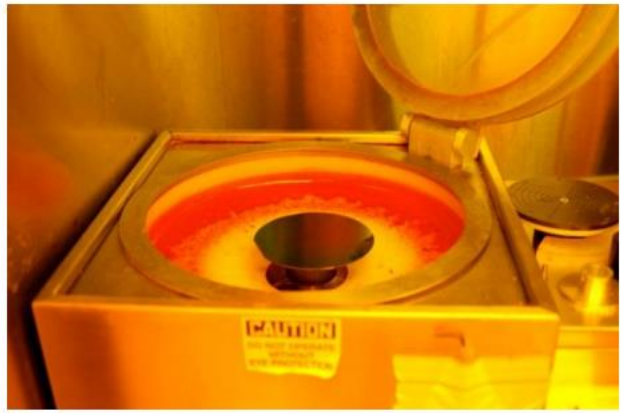

- Rinsing with acetone and IPA, blow dry with $N_2$ for clean wafers to remove resides on the surface
- Dehydration to remove moisture content from wafer

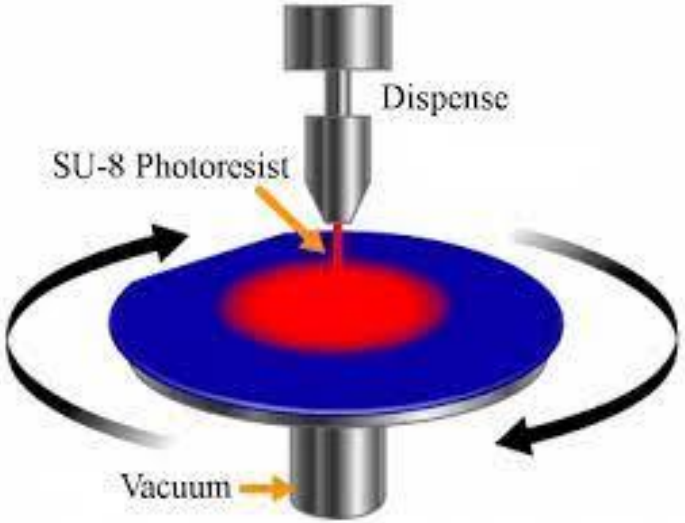
Drying at 200°C for 30 minutes

# Fabrication of Microfluidic Device

## 3. Spin-coating of photo-resist


Spin coater

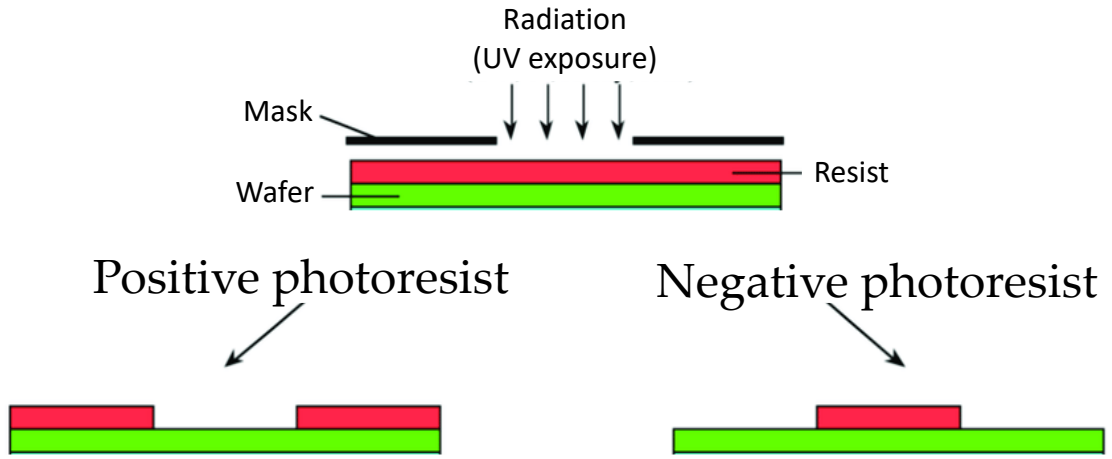





30μm thickness SU8
(2500 RPM, 40 sec)

# Fabrication of Microfluidic Device

## Spin-coating of photoresist…contd.



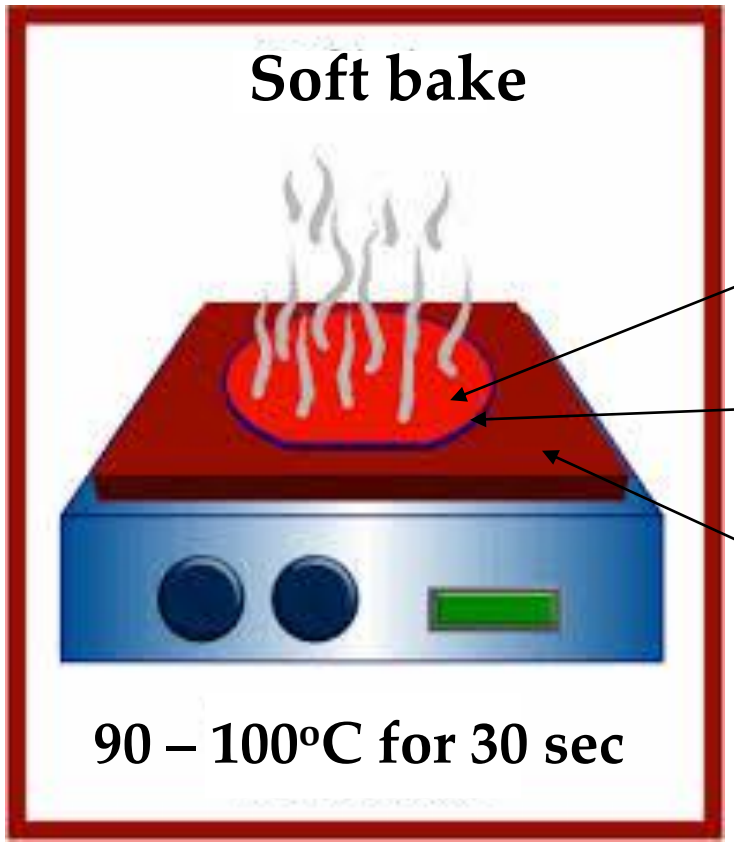

Two types of photoresists

1. Positive photoresist - portion of the photoresist that is exposed to light becomes soluble to the photoresist developer. The unexposed portion of the photoresist remains insoluble to the photoresist developer.

2. Negative photoresist - portion of the photoresist that is exposed to light becomes insoluble to the photoresist developer (cross-linked). The unexposed portion of the photoresist is dissolved by the photoresist developer - SU8

# Fabrication of Microfluidic Device

## 4. Pre-exposure soft bake on hot plate




Photoresist

Wafer

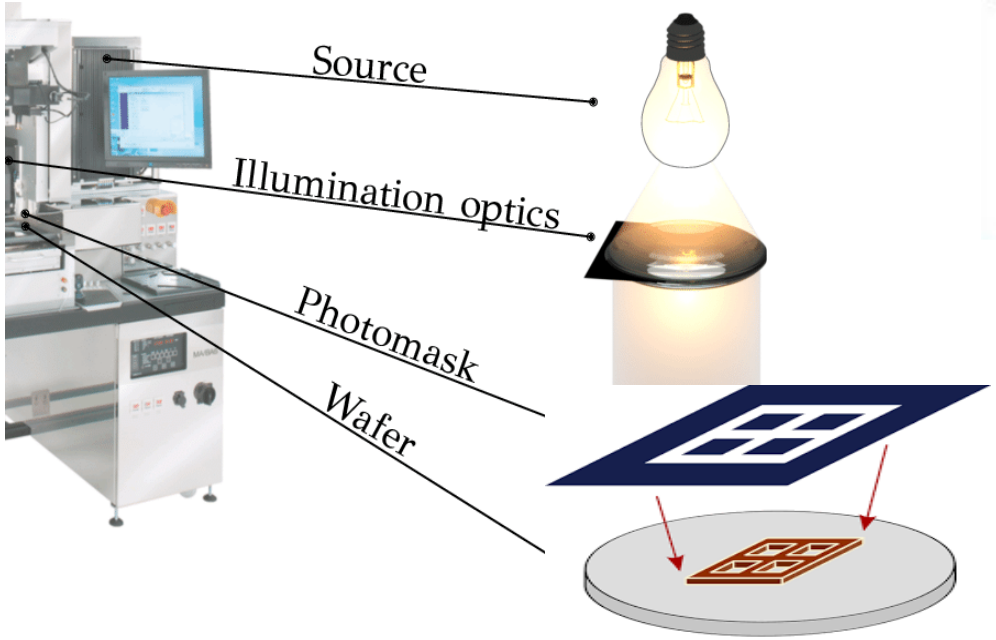
Hot plate

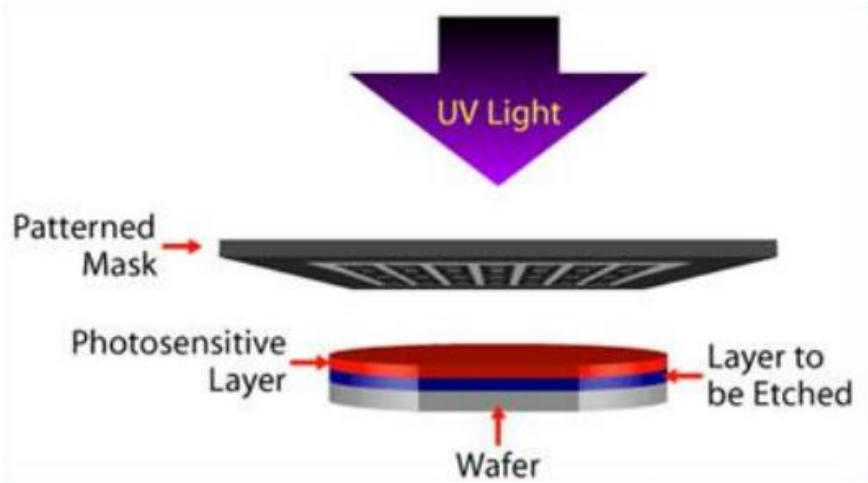
- to bake off the remaining solvents

# Fabrication of Microfluidic Device

## 5. UV Mask-alignment

UV Mask Aligner

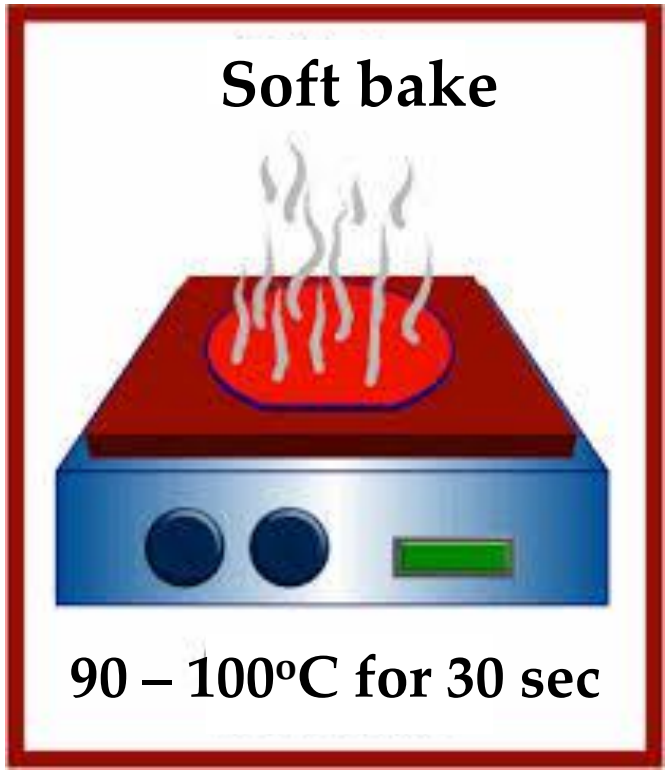



Transfer of geometric design from an optical mask to a light-sensitive photoresist coated on the wafer

# Fabrication of Microfluidic Device

## 6. Post-exposure soft bake on hot plate

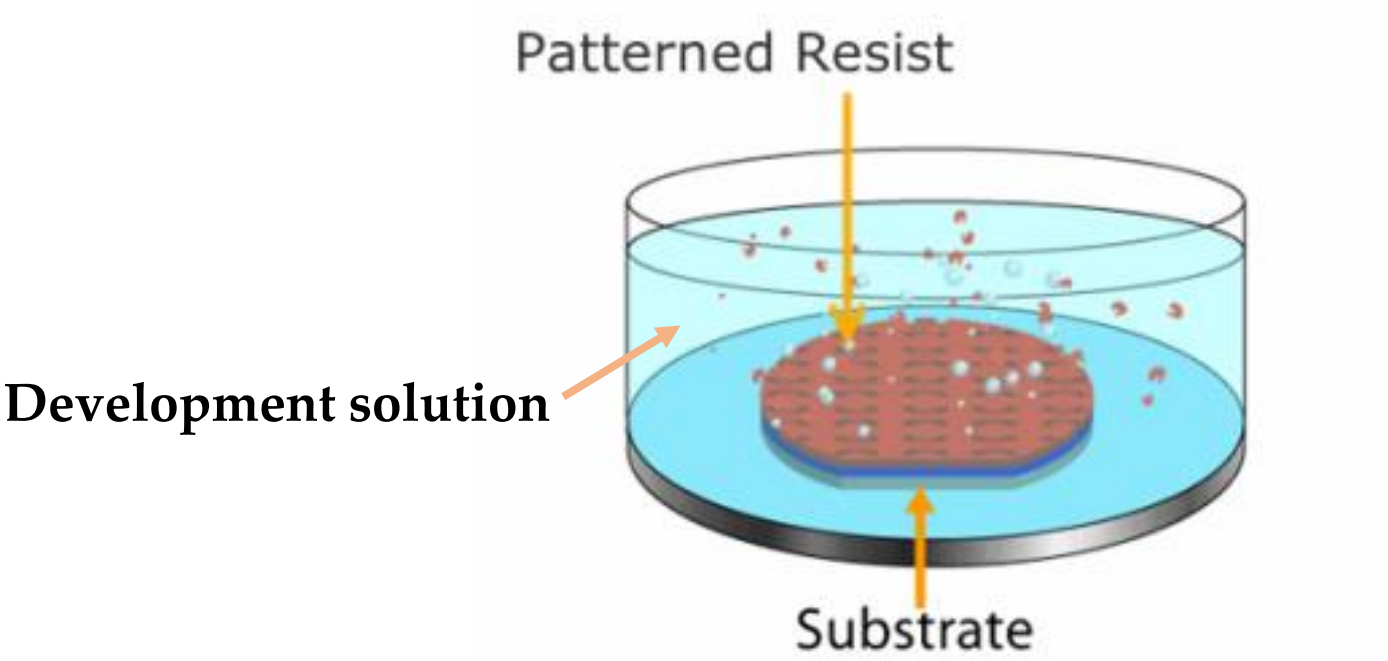




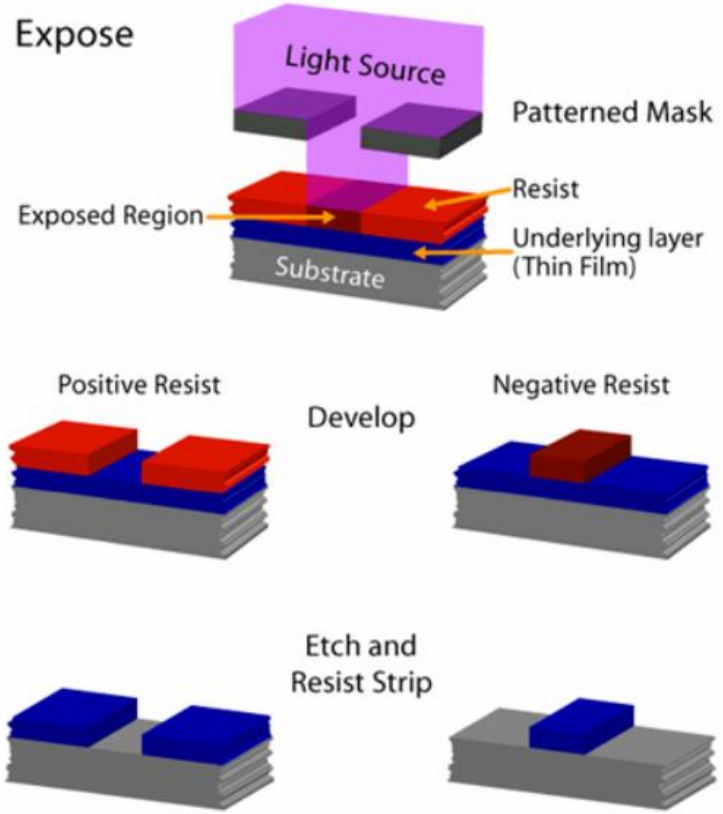
- Performed immediately after exposure
- Completes the photo reaction initiated during exposure
- Same procedure as the pre-exposure soft bake:
  - T = 95 °C on hot plate
  - t = 2 min
  - Cool to room temperature

# Fabrication of Microfluidic Device

## 7. Development (Wet chemical etching)



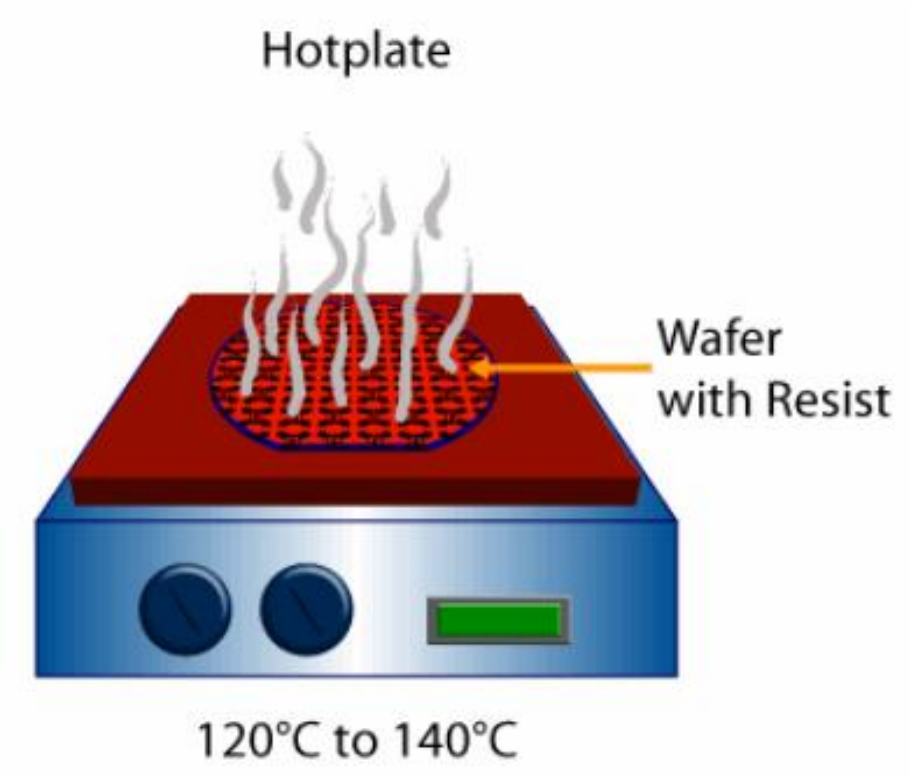

Dissolution of un-crosslinked photoresist in development solution (treatment time: 2-3 minutes)




Difference between negative and positive photoresist (Post-development)

# Fabrication of Microfluidic Device

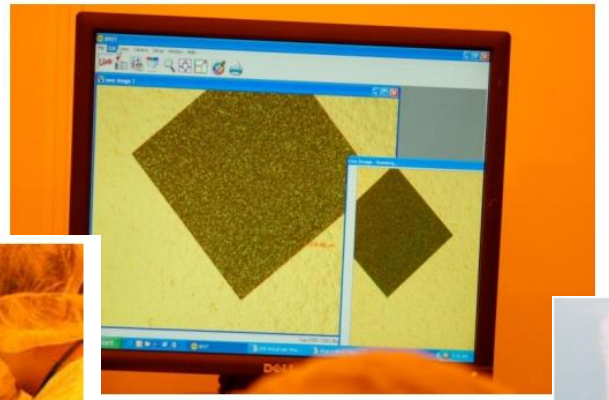
## 8. Hard-bake at 135°C

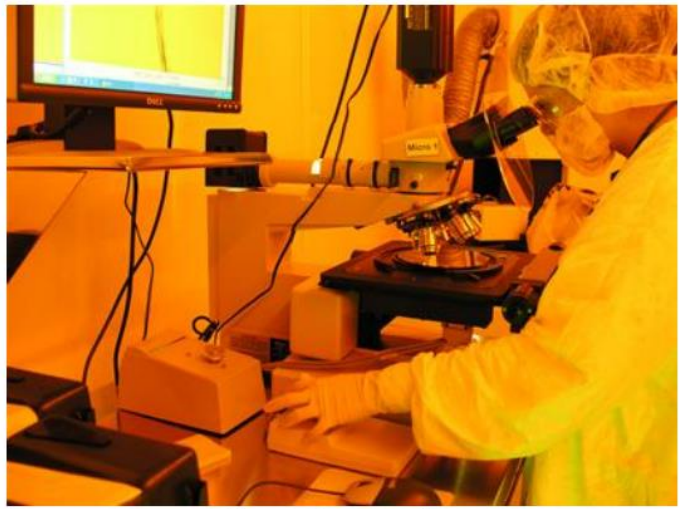



To densify the resist, improve the adhesion to the surface, and make it more resistant to wet chemical etching

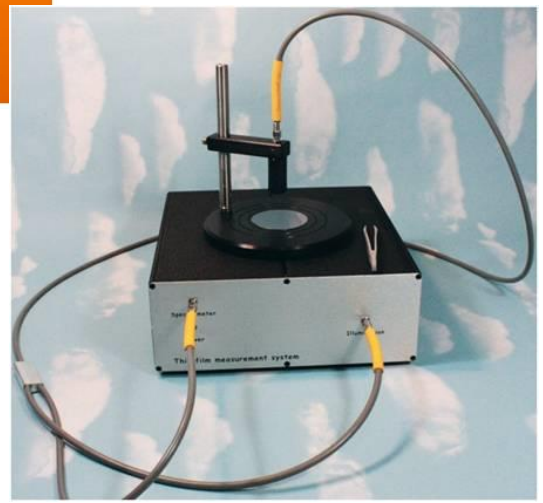
# Fabrication of Microfluidic Device

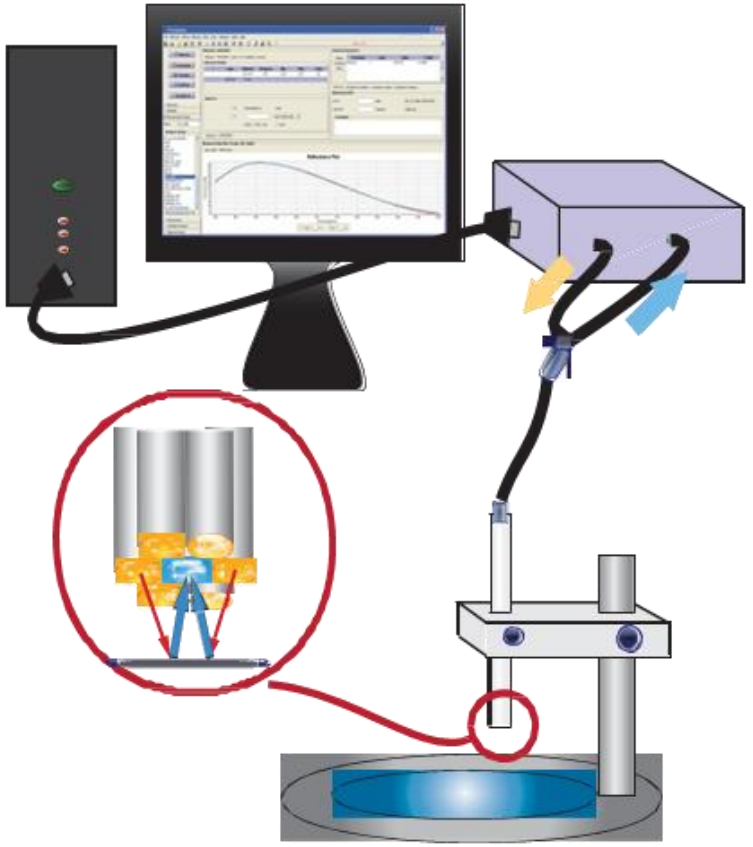
## 9. Inspection of wafer (Thickness measurement)





*Inspecting a wafer*





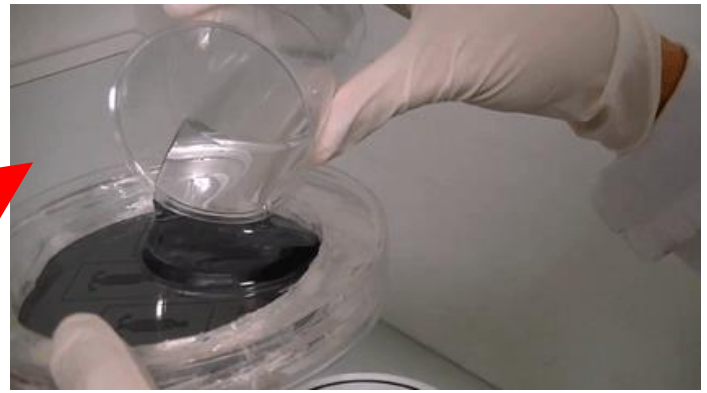
Spectrophotometer/Profilometer/Reflectometer

# Fabrication of Microfluidic Device

## 10. Soft-lithography

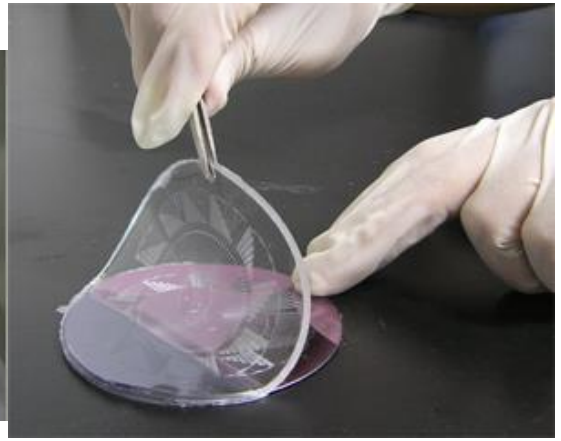
Poly-Dimethyl Siloxane (PDMS) and Curing agent (10:1)

Degassing in a desiccator



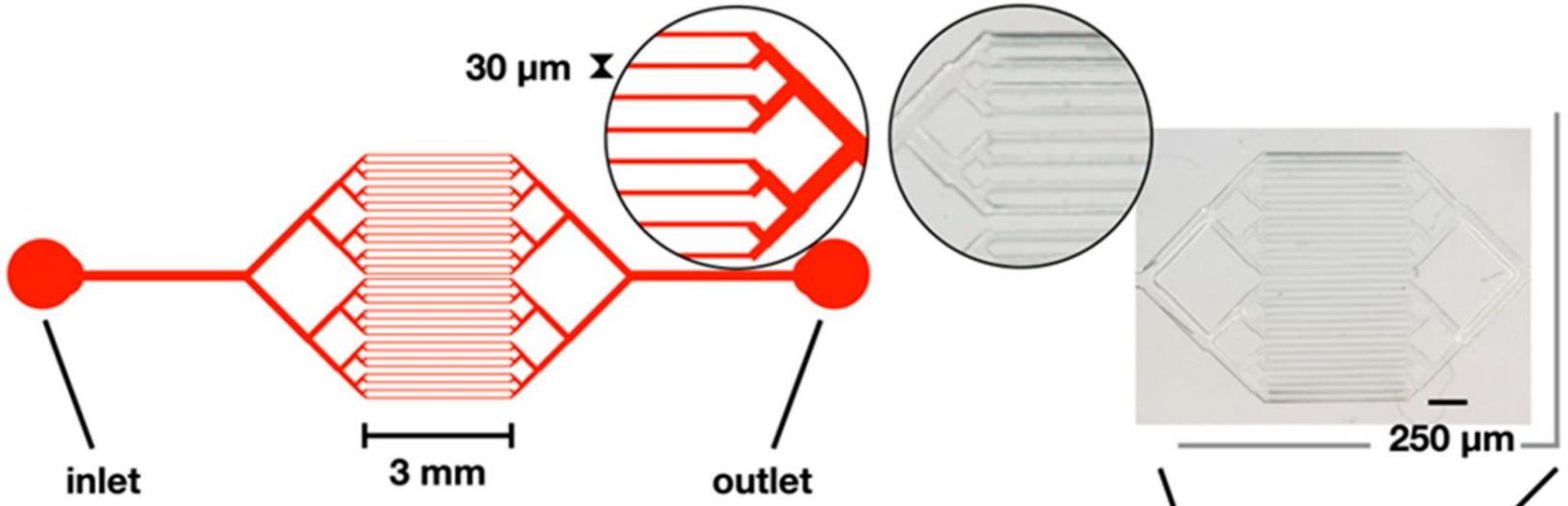
PDMS pouring into a petri-dish containing wafer

Baking for 2 hours at 65$^{o}$C



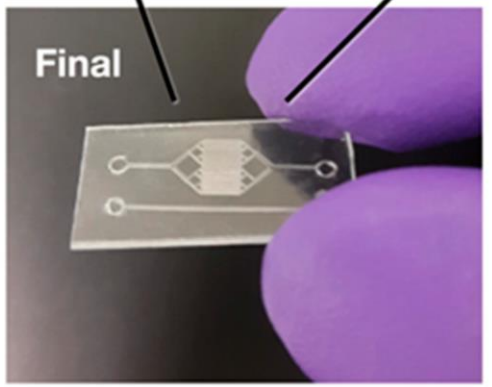
Peeling of solidified PDMS

# Fabrication of Microfluidic Device




**PDMS**

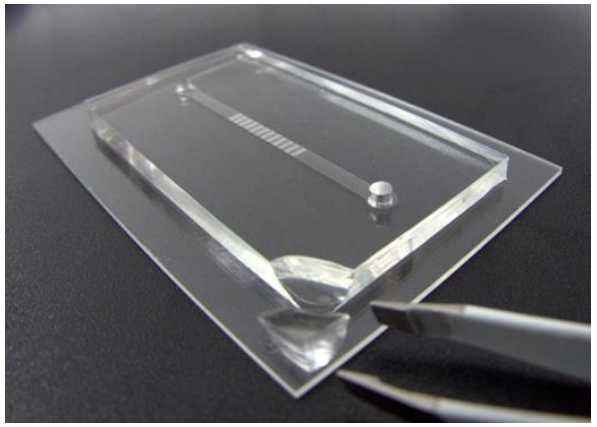
- Inert, non-toxic, non-flammable and transparent
- Widely used material in microfluidic research
- Rapid prototyping with minimal cost
- Requires surface treatment to produce strong bond between surface




PDMS block with embedded micro-channels

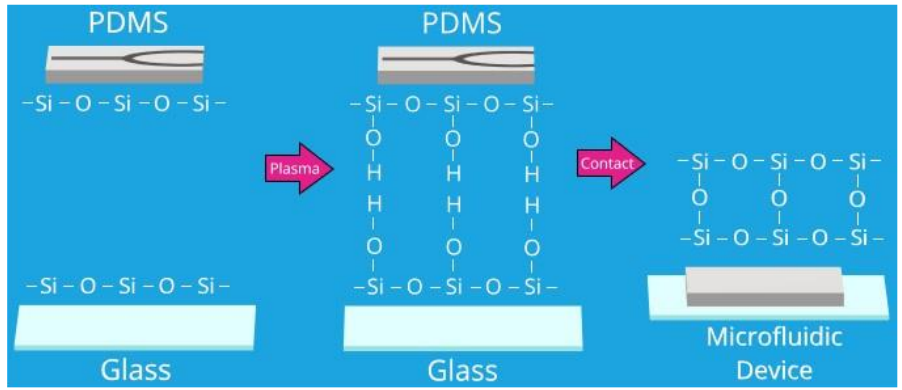
# Fabrication of Microfluidic Device

## 11. Plasma bonding (Air/Oxygen Plasma)



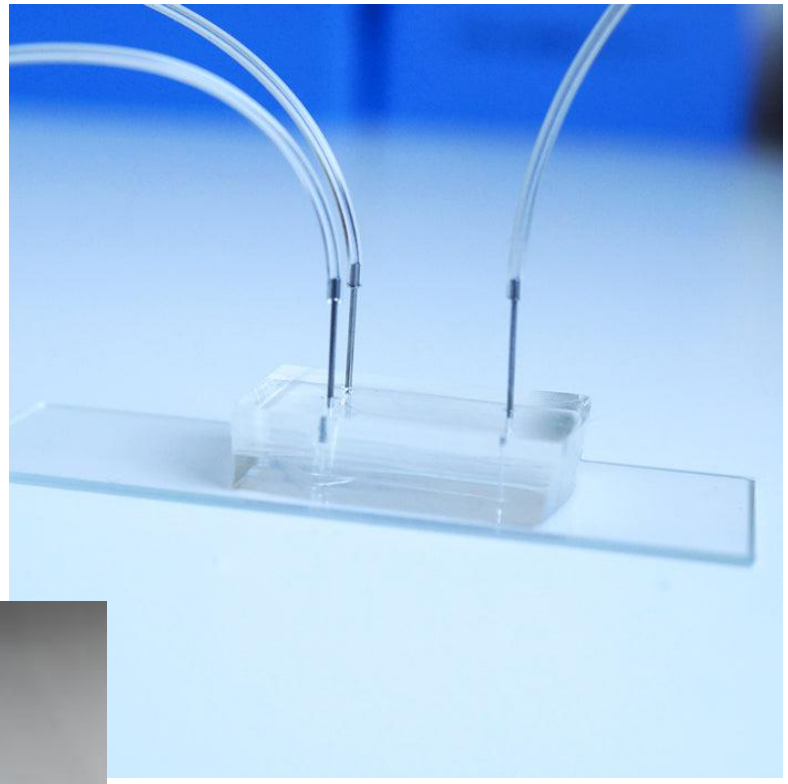
Plasma Cleaner for bonding of hydrophobic surfaces

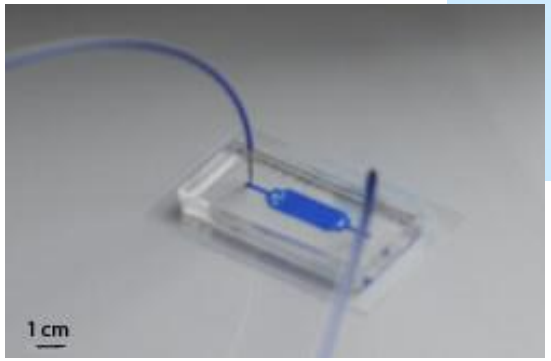
- PDMS surface oxidises in air/oxygen
- Polar Silanol group (-Si-O-H) formation makes surface hydrophilic
- Si-O-Si bond provides strong bonding



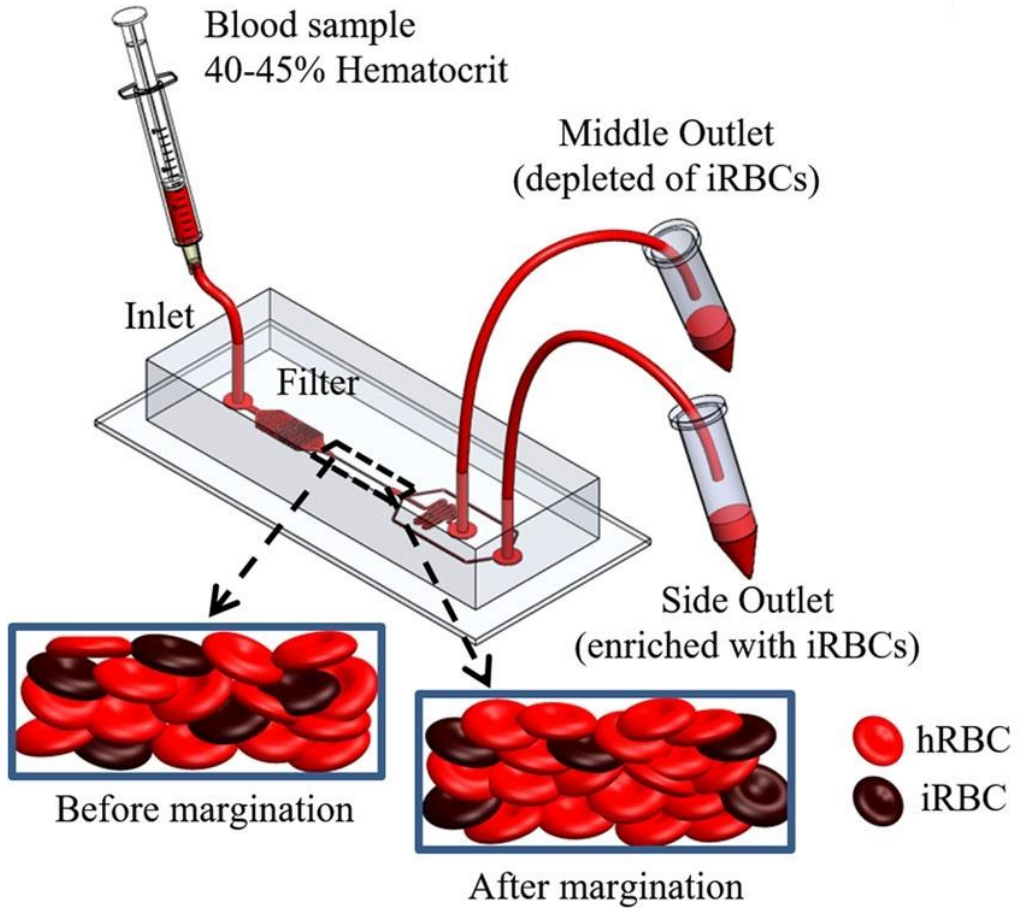

Activation of PDMS and Glass surface

# Fabrication of Microfluidic Device





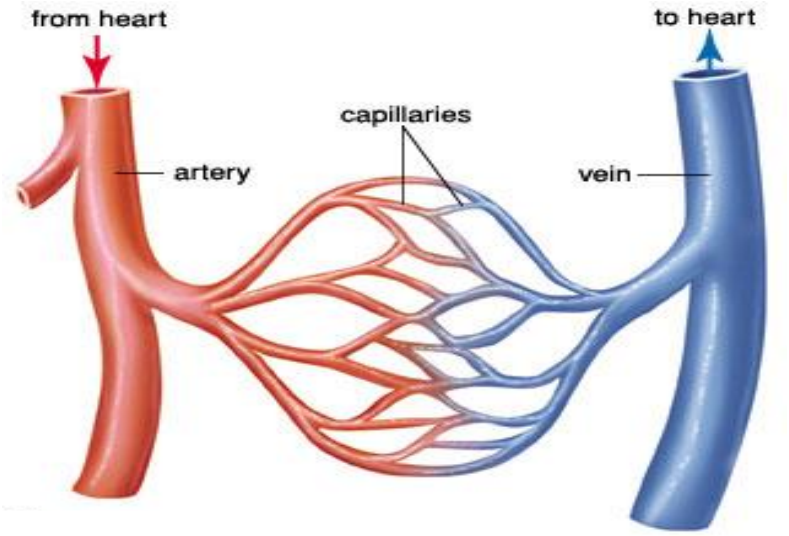

Microfluidic device with inlet and outlet

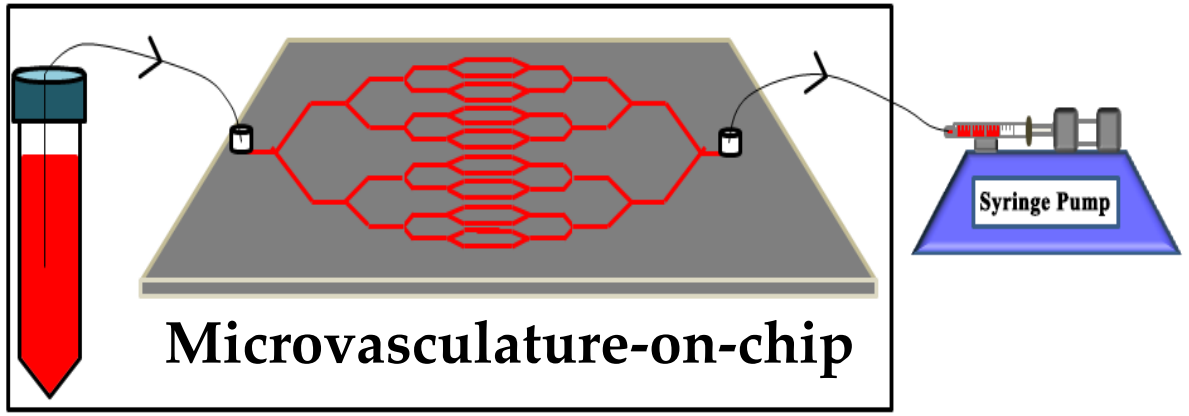


# Relevance in Biological Systems

- Cell manipulation (cell response to different biophysical processes)
- Cell separation and sorting
- Drug administration
- Disease detection
- Macromolecular analysis

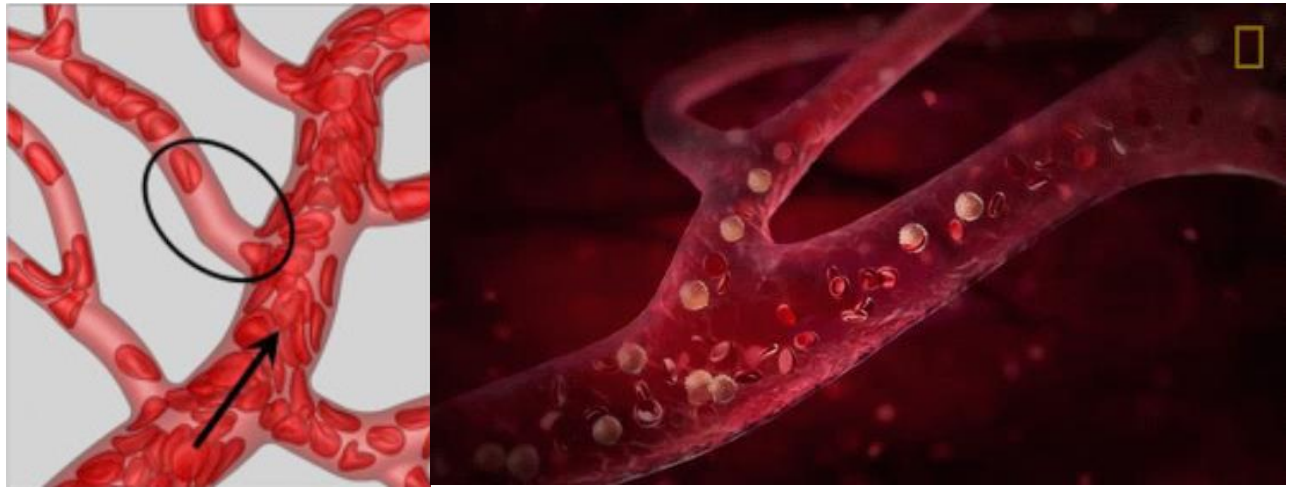
# Biomimetics in Lab-On-Chip devices

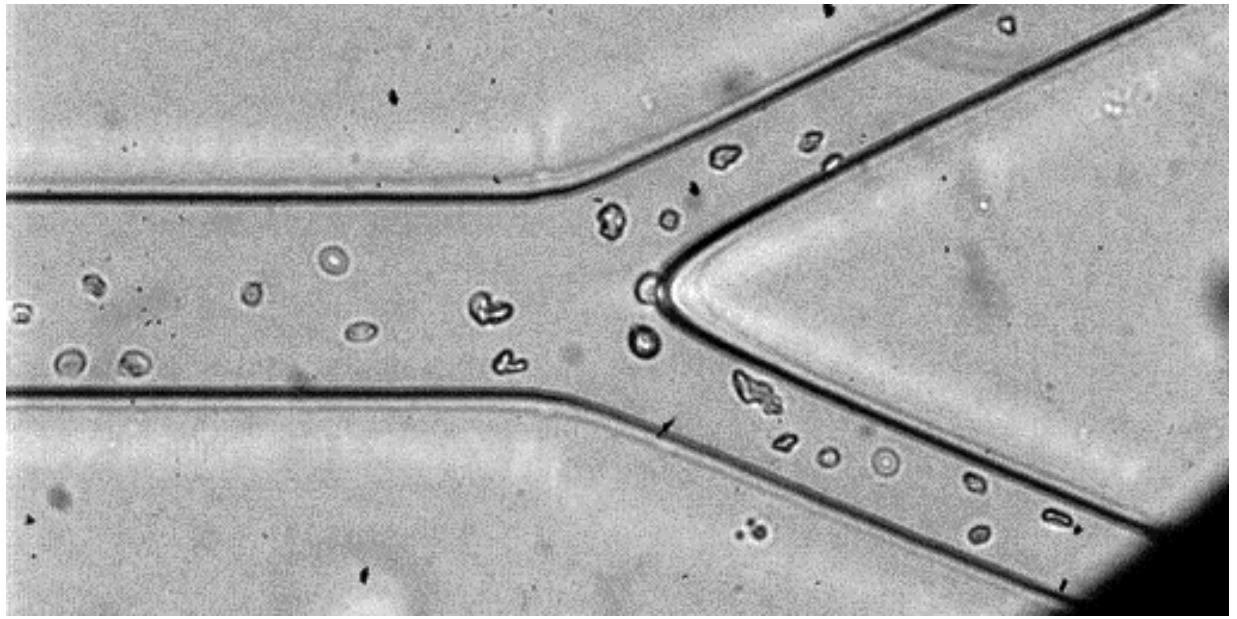


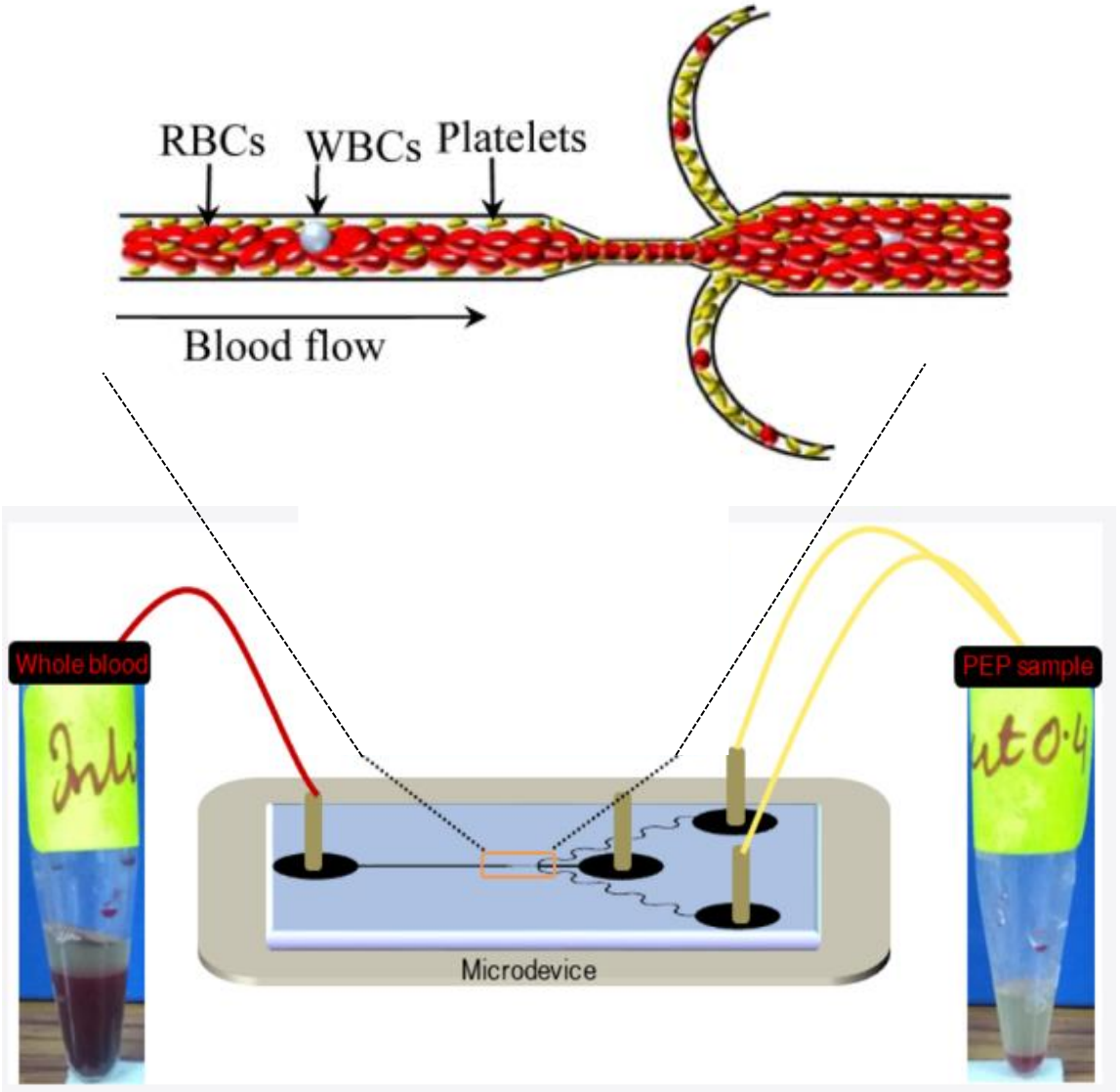

Microdevice that mimics human microvasculature

# Cell manipulation in Microdevice



# Separation of Platelets from Whole Blood using Microdevice



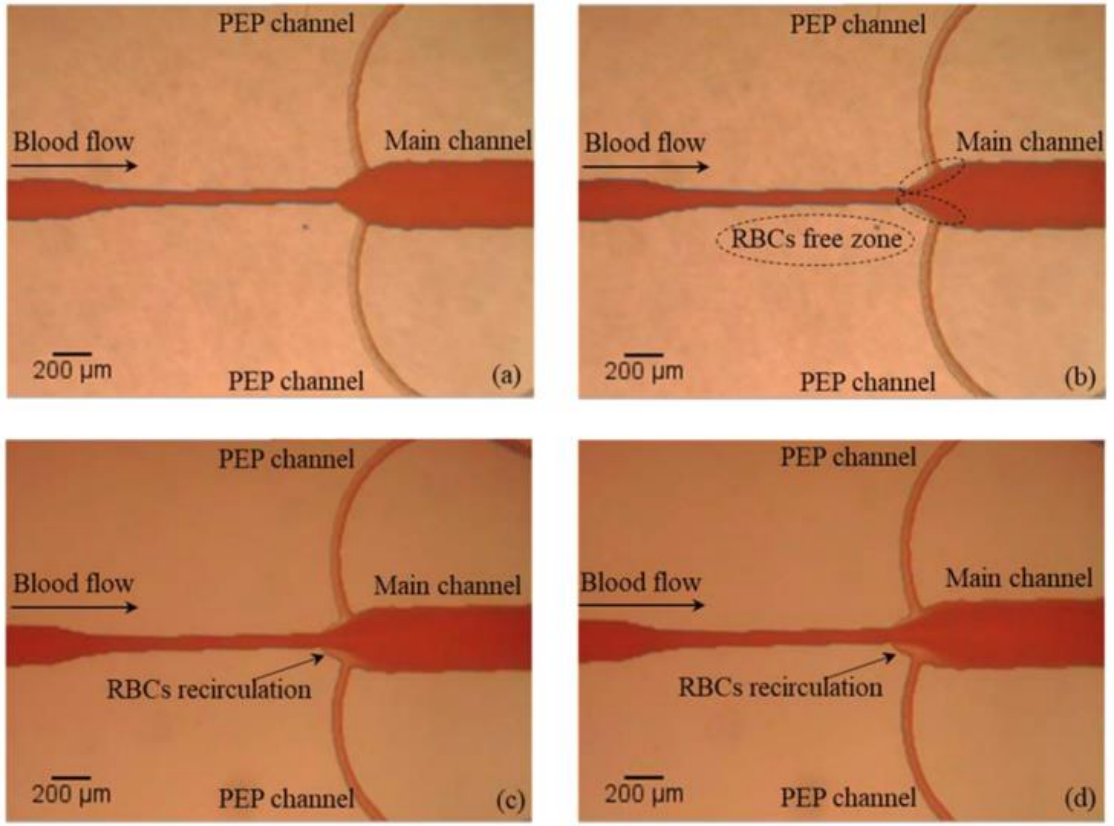
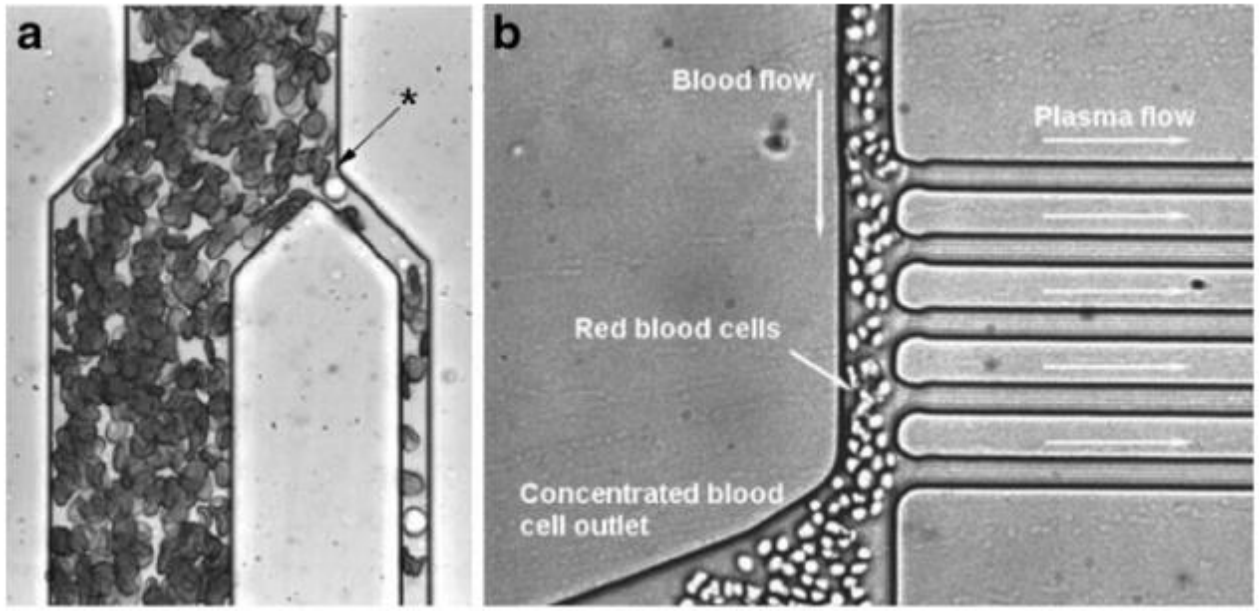




**Figure 5.** Experimental image of microdevice #2 with the whole blood sample at (a) 0.2 mL/min, (b) 0.4 mL/min flow rate, (c) 0.5 mL/min, and (d) 0.6 mL/min.

(Laxmi V, et. Al., I&EC Research, 2020, 59, 4792-4801)

# Separation of WBCs and Plasma from Whole Blood using Microdevice



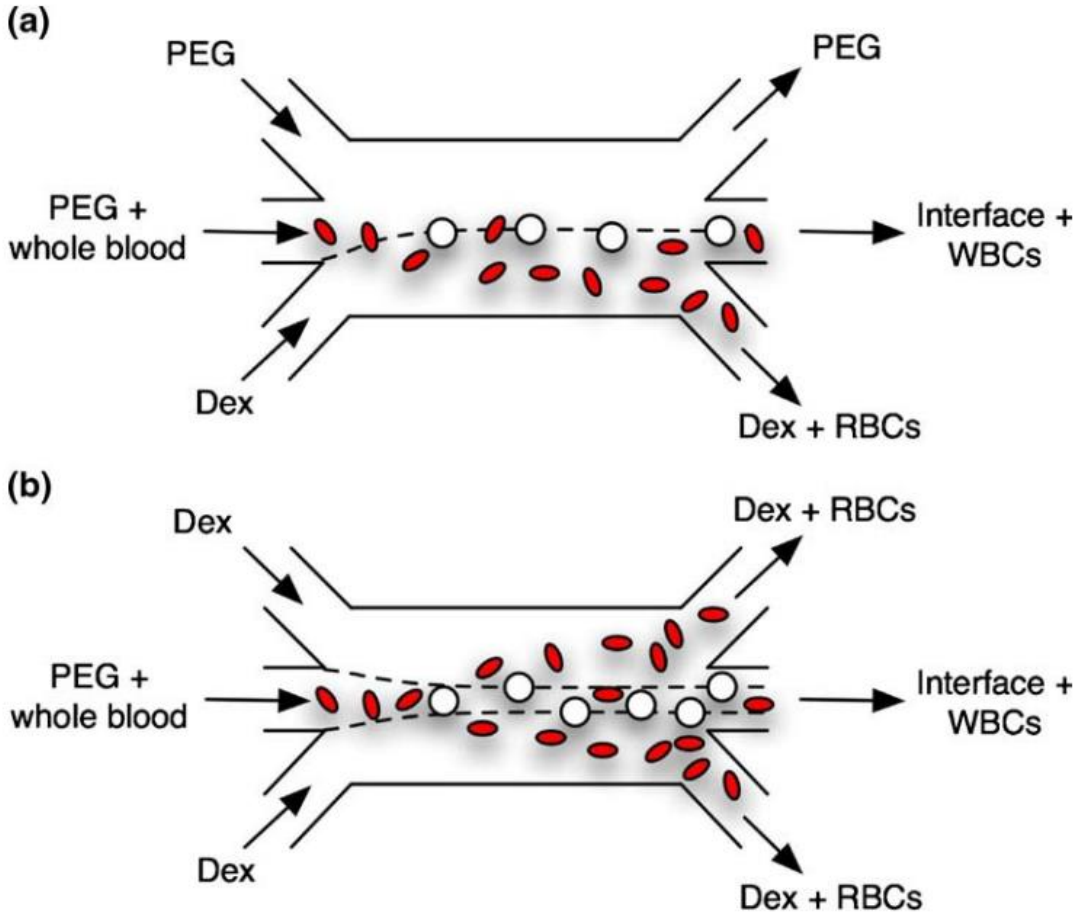

Leukocyte margination is used to separate leukocytes

(Gossett, D. R. et. al., Anal Bioannal Chem, 2010, 397, 3249-3267)

# Separation of WBCs and RBCs from Whole Blood using Microdevice

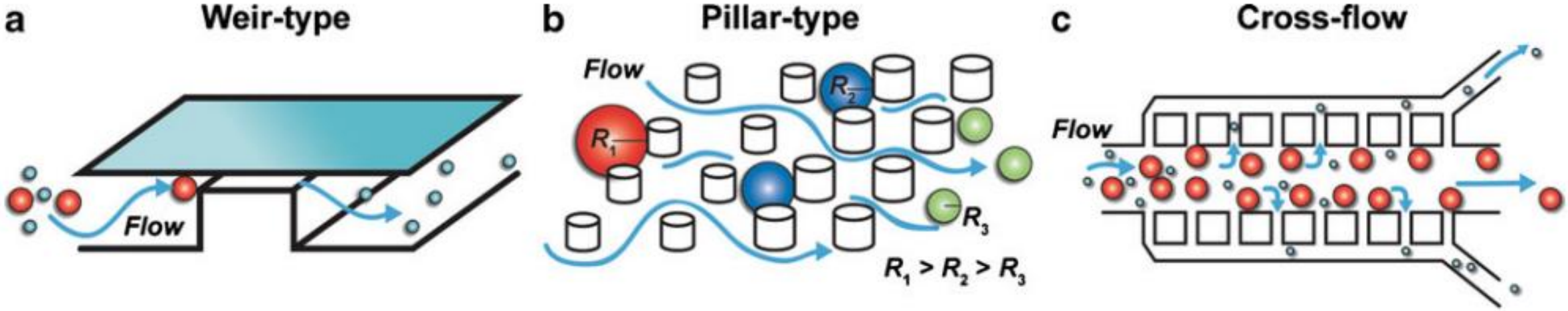
(a) The leukocytes (WBC) prefer the interface while erythrocytes (RBC) migrate to the Dex.

(b) Increases in the surface area that blood is exposed to due to two stream interface, resulting in more effective leukocyte concentration




(SooHoo et al. Biomed microdevices 2009, 11, 323-329)

# Cell-Separation from Whole Blood using Microdevice of different pattern



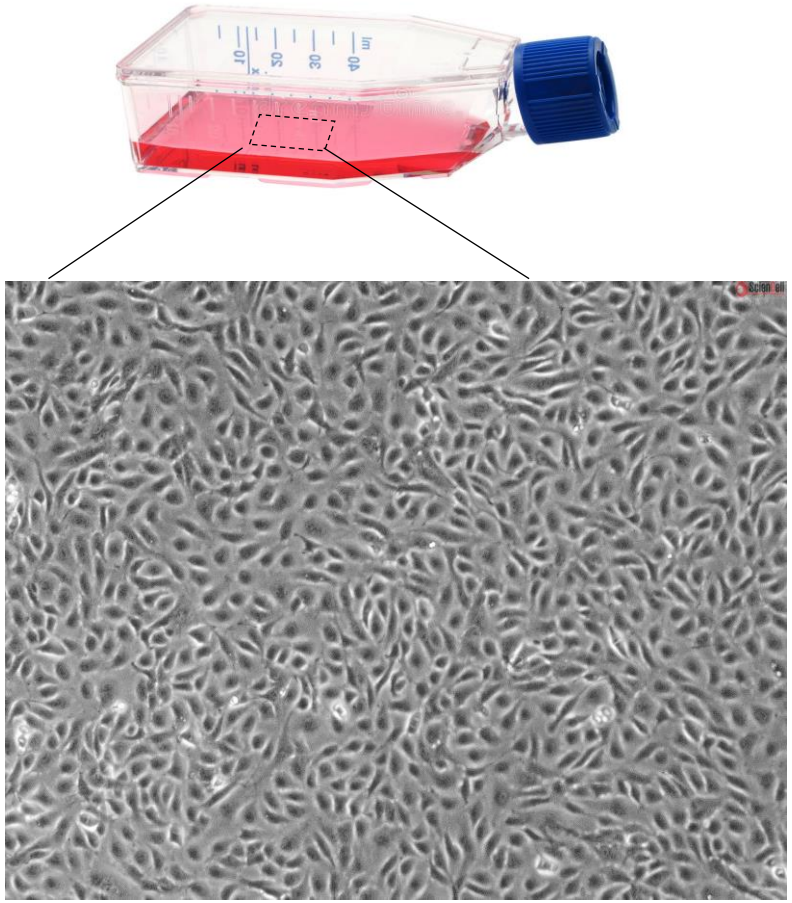

Filters size-exclude cellular components while allowing flow of smaller cells and molecules to pass through a planar slit.

Filters are arrays of pillars which exclude cells larger than the spacing of the pillars

Filters are arranged perpendicular to primary channel flow to avoid problems associated with obstructed flow

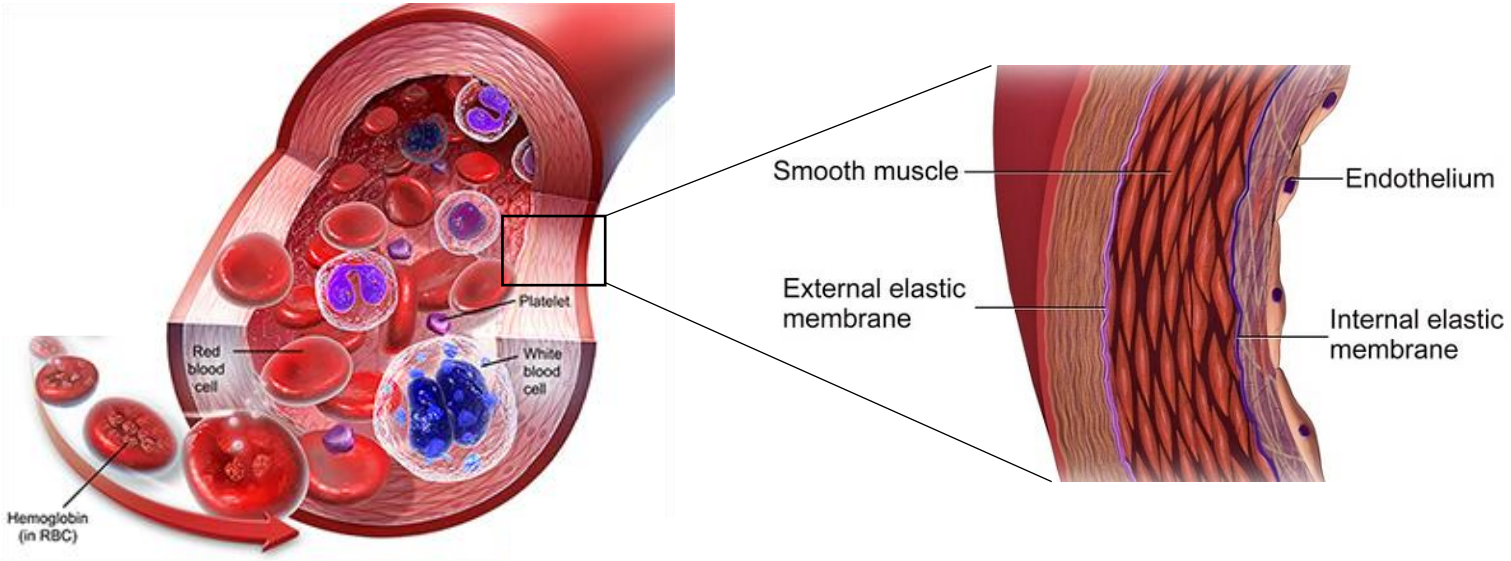
(Gossett, D. R. et. al., Anal Bioannal Chem, 2010, 397, 3249-3267)

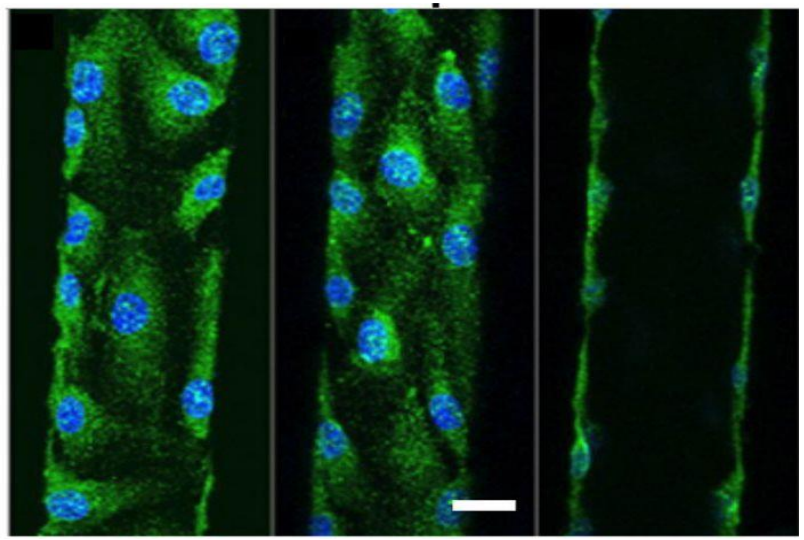
# Replacement for Static Cell Assessment

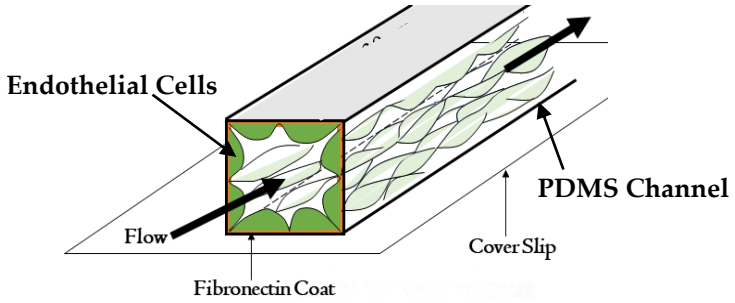


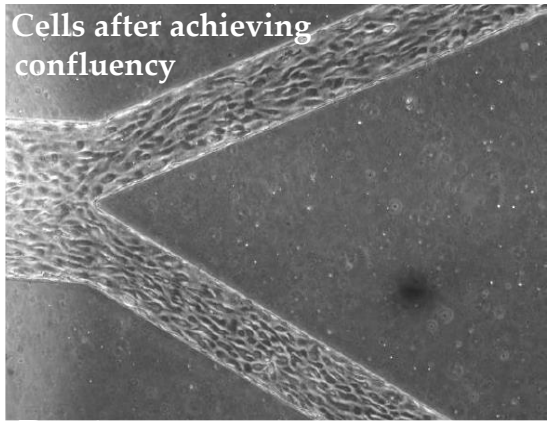
Transwell assay for biological manipulation

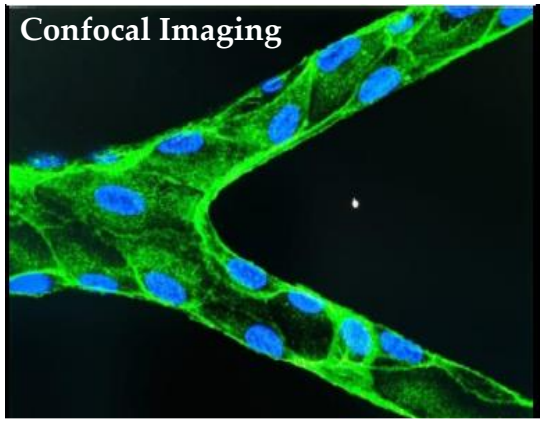
# Epithelial cell culture in Microfluidic devices



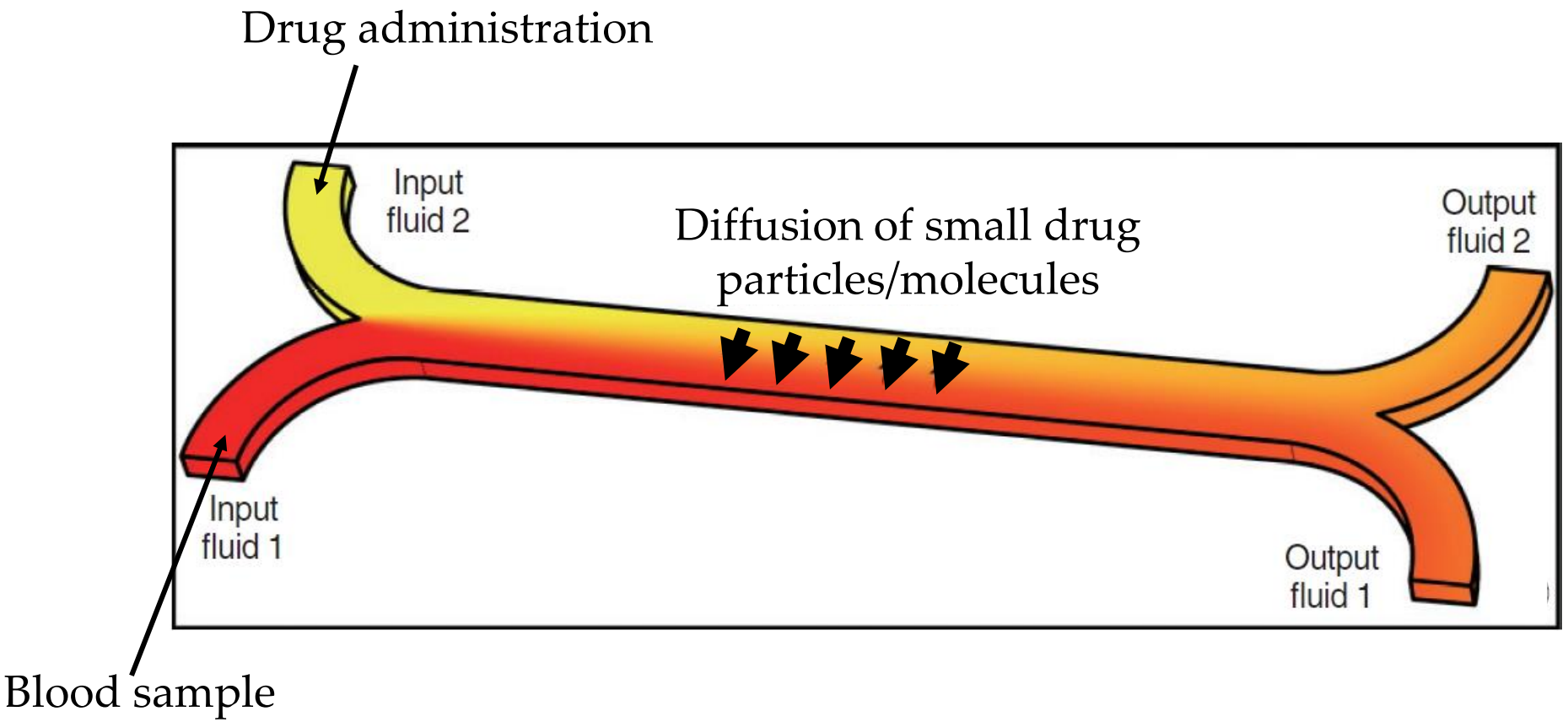





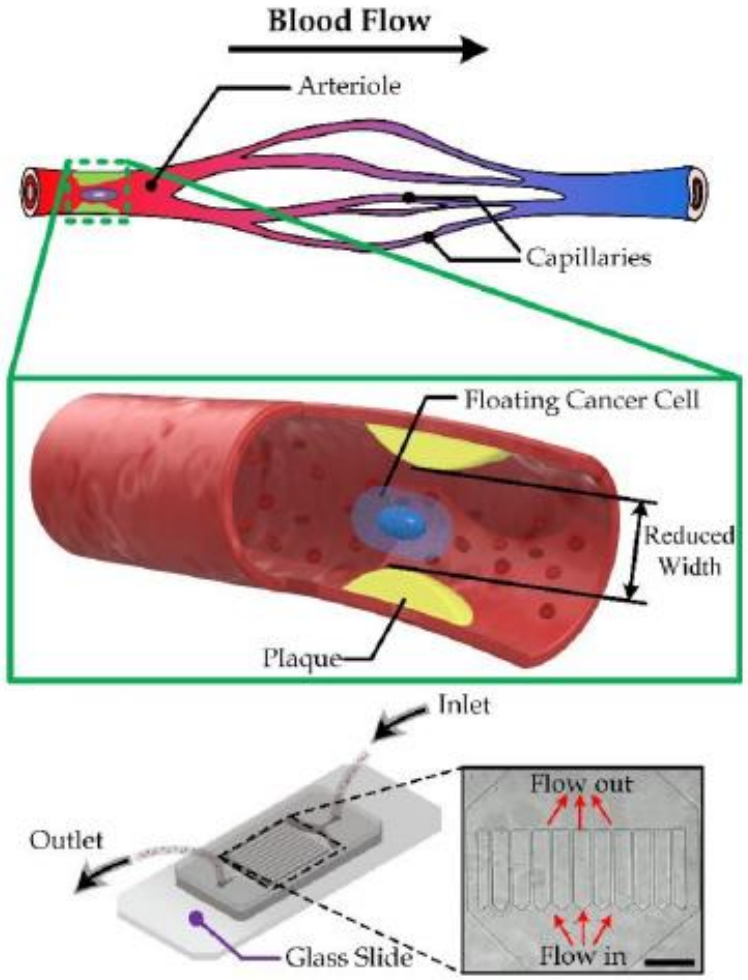



# Drug Testing in Microdevices



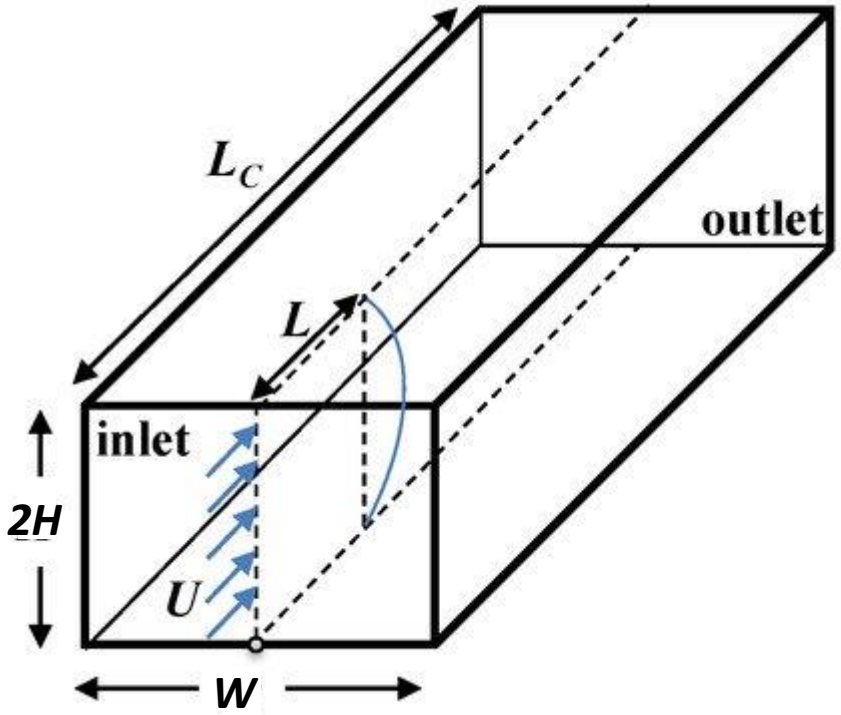
# Analysis of transition speed of floating cancer cells during metastasis

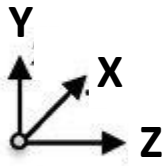



(Ren J, et.al, Micromachines, 2021, 13, 183)

Estimation of transiting speed of a deformed cell passing along a constricted narrow channel.

# Governing Equation for Microfluidic Flows

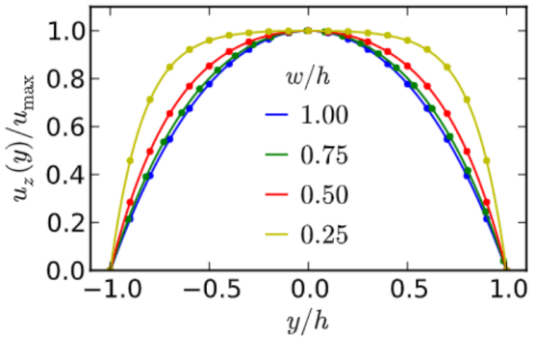


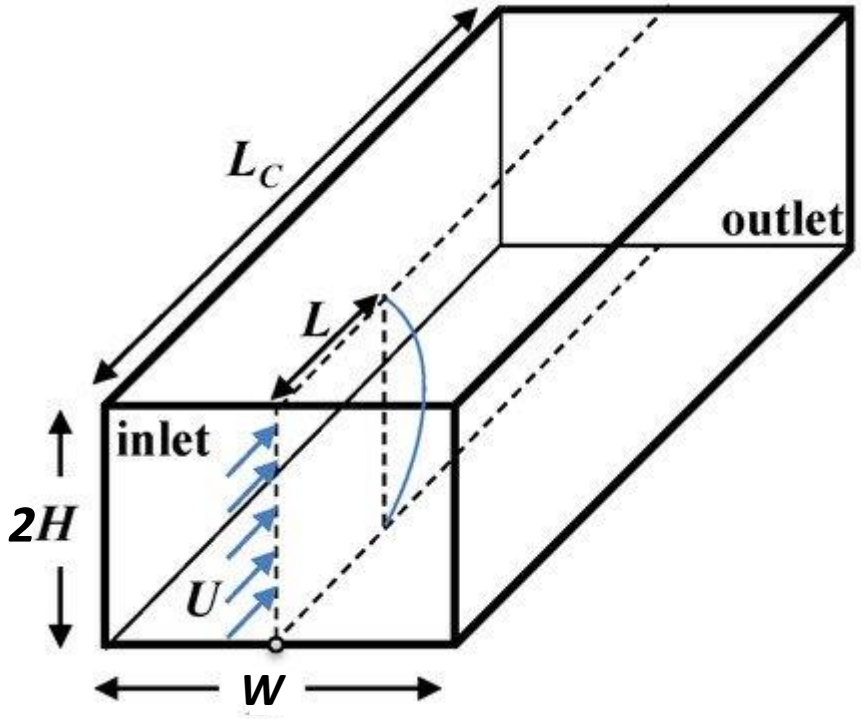

**Velocity profile for fluid flow through micro-channel due to pressure difference:**

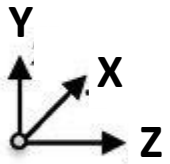
$$U(y) = \frac{\Delta P}{2\mu L_c}(H^2 - y^2)$$

Where,
ΔP – Pressure difference across the two ends of the channel
H – Height of the channel
μ - Fluid viscosity
$L_c$ – Channel length



# Governing Equation for Microfluidic Flows




**Volumetric flow rate through the micro-channel:**

$$Q = \frac{2}{3}\left(\frac{\Delta P}{L_c}\right)\frac{H^3 W}{\mu}$$

Where,

W = Channel width

**Average velocity:**

$$\bar{v} = \frac{Q}{2HW}$$

Thank you