UIC ECE Nanotechnology Core Facility

Nano-Fabricated Extracellular Matrix Topography could Alter the Cancer Cell Behavior

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INTRODUCTION

This research brings together a team of interdisciplinary scientists for transformative research and represents an ideal integration of expertise in cancer cell biology (Dr. Sarah Glover, UIC College of Medicine), cellular biomechanics and multimodal imaging (Dr. Michael Cho, UIC BioE) and state-of-the art fabrication (Ph.D student Kasun A. Gardiye Punchihewa, Dr. An and Dr. Metlushko, the Nanotechnology Core Facility, UIC COE).

This research revolutionizes the current understanding of the impact of extracellular matrix (**ECM**) on cellular biomechanics and behavior. It is believed that the ECM architecture profoundly affects cellular functions and behaviors [1] in ways that are currently unknown or poorly understood. Recognizing that the natural ECM is typically composed of topographical features of multiple length scales (e.g., nanometer to micrometerm), we propose to characterize, engineer and fabricate the biophysical structures and thus recapitulating the in vivo natural tissue environment.

The team involved in the cutting edge engineering and micro, nano-biotechnology research to characterize, understand and regulate the length scale dependent cellular and biomechanical responses. Results from the proposed work are expected to lay foundation and pave the way to potentially revolutionized the cancer research by offering a new framework for dictating and controlling the cell fate, which leads to new cancer treatment modality.

- ***Our initial results indicate that the ECM microtopography regulates the cancer cell differentiation and invasion* [1].**

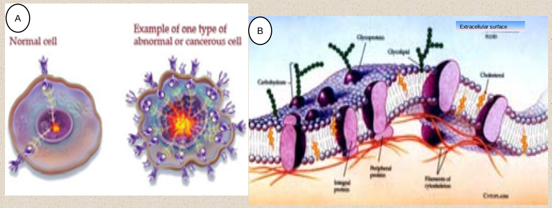


Figure 1: Difference between normal and cancer cell (A) (http://cornellchem.wikispaces.com), interaction of proteins inside the ECM (B).

AIMS

- Characterize the colon tumor ECM architecture and, second, to systematically reproduce these features (in nanometer and micrometer scale) using state of the art fabrication technique such as 3D Electron Beam Lithography (EBL).
- The characterization of ECM architecture has been achieved using scanning electron microscope (SEM) and nonlinear second harmonic (SHG) imaging microscopy of human colon tissue.

METHODS

- Direct writing on a surface is the most fundamental step in any nano and micro structure fabrication.
- The EBL system is a flexible and an ideal solution for patterning of any surfaces in engineering, bio, medical, micro-optics and micro fluidics which requires a resolution better than 50nm.
- The design process for these structures is supported by conversion software specifically designed for these 3D structures.

RESULTS

- Fabrication of ECM topographies which mimics the colon tissue, initially done by 2D EBL to reproduce the main features of ECM.
- The E-Beam lithography could be employed to fabricate "simple" 3D patterns as shown in figure 2A-B. The exposure dose for such 3D applications is selected to be large enough that the exposure-sensitive resist is completely exposed during writing process.
- Surface roughness introduced by adding a grid all over the 100 µm ×100 µm area.

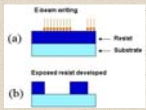


Figure 2 : The standard steps on direct writing on the surface fabrication process: Resist is locally exposed by electron beam (a), exposed resist removed chemically (b).

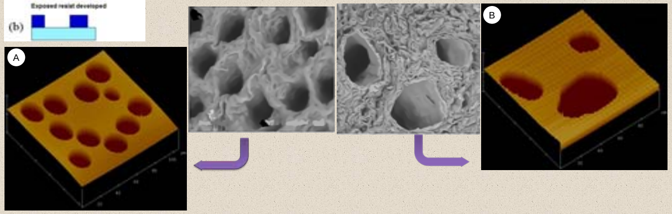


Figure 3A-B: 3D Atomic Force Microscopy images of fabricated ECM's corresponds to two different stages of colon tissues.

- The *state-of-the-art 3D fabrication* could be achieved by modulating the exposure dose as shown schematically on figure 4.
- After a chemical wet-development process which removes the areas with higher dissolution rates (the exposed areas in case of a positive resist) the desired 3D profile could be achieved (fig4b).

Figure 4: 3D patterning EBL writing protocol , exposed the resist point by point with different dose corresponding to the dose matrix (a), resist development and 3D profile creation (b), adding solution mixture of PDMS and curing (c), Release the PDMS and produce the 3D scaffold which replicates the ECM.

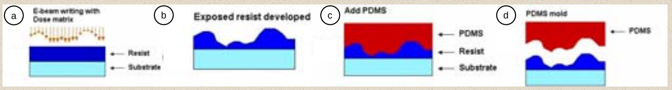
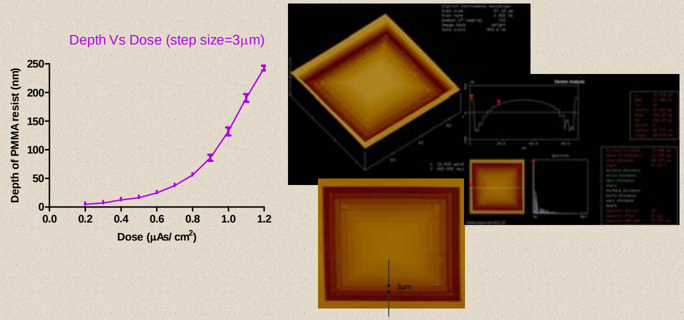


Figure 5: Atomic Force Microscopy (AFM) images of fabricated 3D structures. 3D pyramids fabricated in Poly (methyl methacrylate) (PMMA) polymer by electron beam exposure with different doses as shown schematically in figure 6. PMMA is FDA approved.



- 3D dose pyramids were created with different step sizes of 1 µm,2 µm & 5 µm.

RESULTS

PMMA aspect ratio α function(exposure dose)

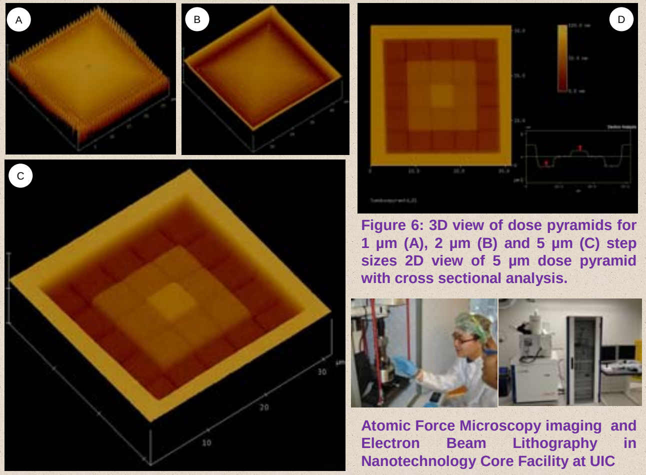
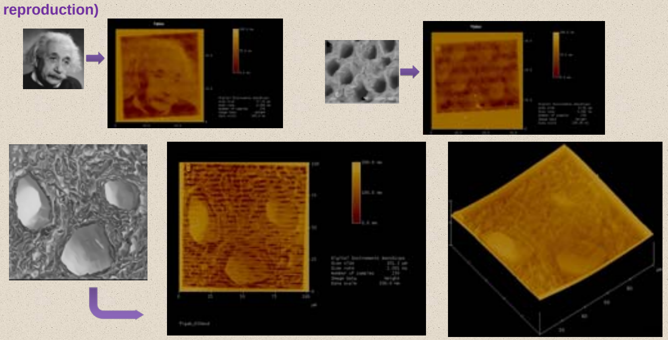


Figure 6: 3D view of dose pyramids for 1 µm (A), 2 µm (B) and 5 µm (C) step sizes 2D view of 5 µm dose pyramid with cross sectional analysis.

Atomic Force Microscopy imaging and Electron Beam Lithography in Nanotechnology Core Facility at UIC

- One-to-one 3D fabrication can be done by directly converting the grayscale image to dose matrix using conversion software.

Figure 7: Atomic Force Microscopy images of fabricated 3D structures (one-to-one ECM reproduction)



CONCLUSION

- Highly accurate 3D biological structures can be reproduced using state of the art 3D Electron Beam Lithography available in the NCF at UIC.

REFERENCE

1.) Rebecca Rapier,Jameela Huq, Ramana Vishnubhotla, Marinka Bulic, Cecile M Perrault, Vitali Metlushko, Michael Cho, Roger Tran Son Tay, Sarah C Glover. *Cancer Cell International* 2010, **10**:24