Microfluidics-assisted Photo Nanoimprint Lithography for the Formation of Cellular Bioimprints

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Bioimprint is a technique capable of permanently capturing a replica impression of biological cells for use in high-resolution imaging and analysis[1]. Beyond imaging, the capability to form imprints with nanometer scale biological information is of great potential for cell and tissue culture applications. For example, pre-patterned cell-culture scaffolds with imprinted cell footprints might 'lock' adhered cells into their natural shape and thus maintain the phenotype of the cells used for the initial imprint[2]. In a step towards scaffold formation, we have recently improved the original *Bioimprint* process by replacing the previously employed elastomers with a fast UV-curing, biocompatible methacrylate copolymer[3]. While this material shows excellent replication fidelity, handling is less straightforward than for the previously used elastomers.

Thus, to enable the repeatable formation of geometrically defined and potentially bioactive cell-culture scaffolds, we have developed a modified *Bioimprint* process based on the use of microfluidics for delivery and removal of the copolymer. In this paper we introduce the process and demonstrate its use for the formation of cell-culture scaffolds. The process (see Fig. 1) uses a custom poly-dimethylsiloxane (PDMS) microfluidic adapter designed for commercially available Transwell® (Corning) membrane insets, which have the potential to increase cell-survival by allowing for continuous cell-media contact from the Basal side. The microfluidic adapter itself was fabricated using soft-lithography and incorporates two micro-chambers (see Fig. 2a). Upon insertion into the inset *Ishikawa* endometrial cancer cells were cultured directly on the Transwell® membrane. For imprinting the cell-culture media in the chamber was replaced with the liquid copolymer and a short UV exposure is used for curing. The solid imprint can then be easily removed from the cells via the PDMS adapter (see Fig. 2b&c). We will demonstrate high-resolution atomic force (AFM) imaging of the cell surface (see Fig. 3) and use of the imprint as a cell-culture scaffold .

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1 J. Muys, et al., J. Nanobiotechnology 4, 1 (2006).
2 B. D. Ratner and H. Shi, Curr. Opin. Solid State Mater. Sci. 4, 395 (1999).
3 F. Samsuri, et al., J. Nanotechnology, accepted for publication.

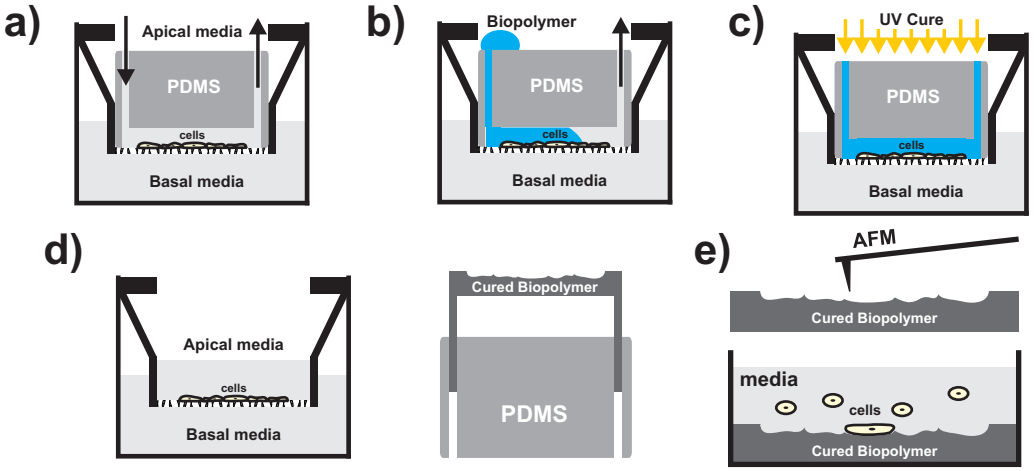

Fig. 1: Schematic of the *Bioimprint* process. (a) Cells to be imprinted are cultured in a PDMS adapter inserted into a Corning Transwell® inset. (b) Apical media is replaced with UV-cureable biopolymer through the adapter. (c) The biopolymer is UV-cured and removed (d) from culture using the PDMS adapter. Cells are re-immersed in media (d) and the *Bioimprint* is removed (e) for imaging and use as a cell-culture scaffold. Cells are in continuous contact with Basal media during the process.

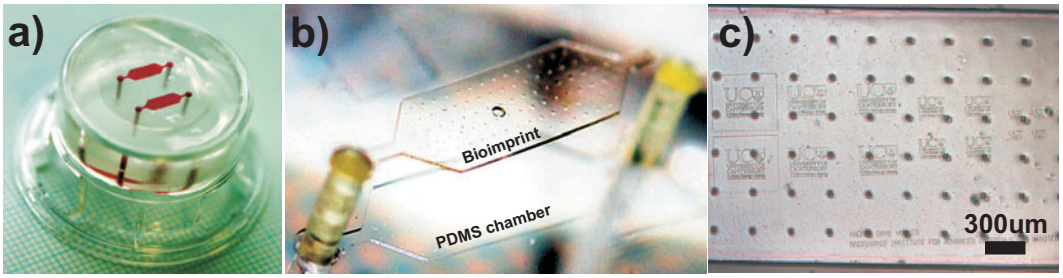

Fig. 2: (a) Photograph of the PDMS adapter device inserted into the Transwell® membrane inset. The cell-culture chamber was filled with red-colored water for visualization. (b) Photograph of the cured *Bioimprint* during removal from the PDMS adapter. (c) Micrograph of a test pattern replicated in the biopolymer. Square holes in the replica correspond to PDMS pillars in the culture chamber of the device.

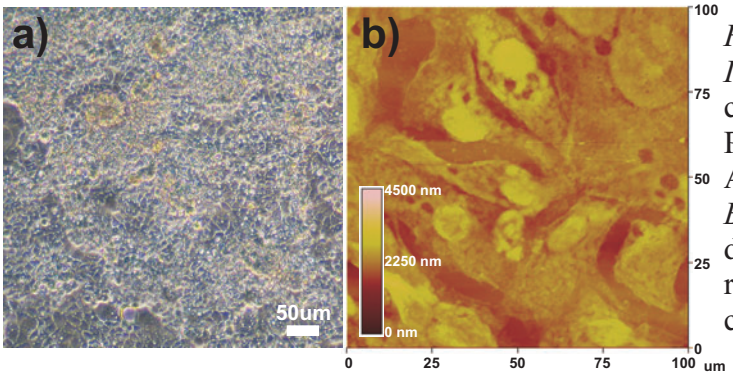

Fig. 3: (a) Micrograph of *Ishikawa* endometrial cancer cells cultured in the PDMS adapter device. (b) AFM micrograph of a *Bioimprint* of cancer cells demonstrating the high-resolution replication capabilities of the process.