Micro/nano devices based on biological models for biomedical applications

P. Guida [a], G. Firpo [a], D. Pezzuoli [a], D. Repetto [a], L. Repetto [a]

[a] Nanomed Labs, Department of Physics, Università di Genova, Italy
e-mail: patrizia.guida@unige.it

Keywords: micro/nano-fabrication, biomimetic device, biomedicine, tissues

In tissue engineering, guiding the cells to differentiate into the right phenotype and in the right place, also requires an environment providing the same factors that govern cellular processes *in vivo*. However, despite the recent advances in terms of developing human tissue and disease models *in vitro*, particularly centered on novel approaches exploring stem cell (SC) technologies [1], the *in vitro* models fail to faithfully reproduce tissue-like complex architectures [2] - especially of those with exceptionally complex morphology such as kidney [3] - or to recreate proper synthetic cell microenvironments such as cancer stem cell niches [4]. These limits prevented the use of models for studying human organ development, realistically modelling diseases and establishing therapeutic treatments. These challenges are of great interest for researchers working on rapid prototyping technologies which can effectively contribute to develop new biomedical techniques, devices and potentially also disease treatments.

Recent advances in 3D printing and soft-lithography techniques have made possible to develop advanced 3D- systems by turning researchers' designs into 3D-printed objects, and to create micro/nano devices with complex custom topographical features made from biocompatible polymers such as PolyDiMethylSiloxane (PDMS) [5] [6]. Thanks to such combined technologies, the development of novel cell culture approaches has improved considerably.

Here, we describe how our research allows biologists to grow human stem cells and tissues under more accurate and in vivo-like conditions. In particular, we report on 3D engineering scaffolds for rapid generation of geometrically predefined kidney units that bona fide resemble normal kidney anatomy and physiology, and that can be used for modeling patient-specific disease and drug testing [7] and, on the development of multi-chamber integrated devices to *in vitro* support long-term culture of patient SC-derived differentiated mammary luminal cells.

This biomimetic approach could be potentially applied to many other cell types to develop into tissues with specific superstructures reproducing the function of a patient-specific organ.

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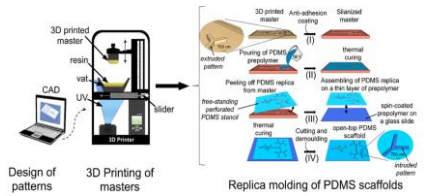

Figure 1. Schematic representation of PDMS fabrication. Designed patterns are converted into 3D plastic masters using stereolithography. Subsequently, extruded patterns of the master are replicated in the PDMS scaffolds through replica molding.

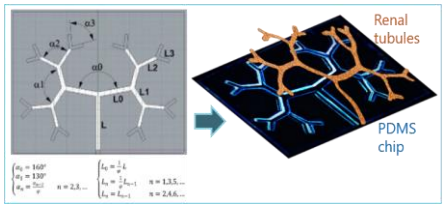

Figure 2. The 'golden fractal tree' formula. The tree-like biomimetic pattern consisting of fractal-like planar ramifications. Cells suspended in collagen are seeded in the biomimetic scaffold and at 2 days, complex tubules self-detach from the scaffold.

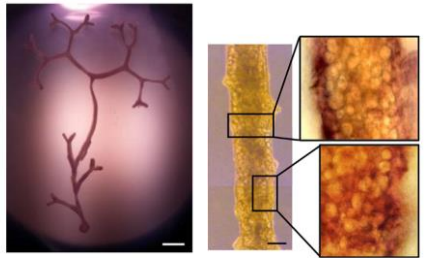

Figure 3. This engineering system is a quick and efficient tool for generating custom-made, functional and anatomically correct tubules, modeling kidney disease, and discovering new drugs, and is also useful for studying human kidney development and individual patient's genetic defects. Scale bars: 2 mm

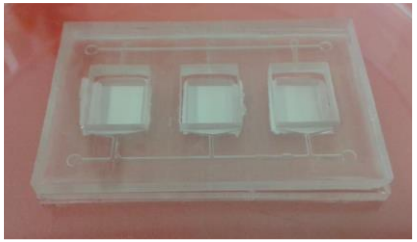

Figure 4. Image of the PDMS multi-chamber device integrating removable porous electrospun matrix with nano-roughness.