Towards Bioactive 3D microenvironments

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The ability to engineer biomimetic surfaces is fundamental for developing more physiologically relevant cell models, which in turn accelerates research in tissue engineering, regenerative medicine, and drug discovery by providing a more accurate platform for studying cellular function.[1]Cells in their natural environment encounter intricate topographies, chemical gradients, and mechanical cues at the micro and nanoscale. To create more accurate in-vitro cell models, it's essential to develop nanofabrication tools capable of mimicking these complex nanoscale features of the cellular microenvironment.

By combining different nanofabrication tools,[2] we develop microenvironments with topographic, mechanical or biochemical cues ad-hoc (Figure 1). **Two-photon lithography**, a 3D printing technique that uses a focused femtosecond laser to initiate polymerization within the laser's focal point, enables the fabrication of complex, arbitrary 3D geometries with submicron precision. With proved capability to pattern soft polymers, it is a valuable tool to mimic the extracellular matrix. **Scanning Probe Lithographic** techniques, conversely, offer the capability to pattern biomolecules (lipids, antibodies, proteins) with nanoscale control. By combining these powerful techniques, we can create sophisticated cell models that enable us to investigate fundamental biological questions, such as the role of membrane curvature,[3] control cell-anchoring points in 3D cultures, [2]and apply precise mechanical stimulation at the nanoscale.[4]

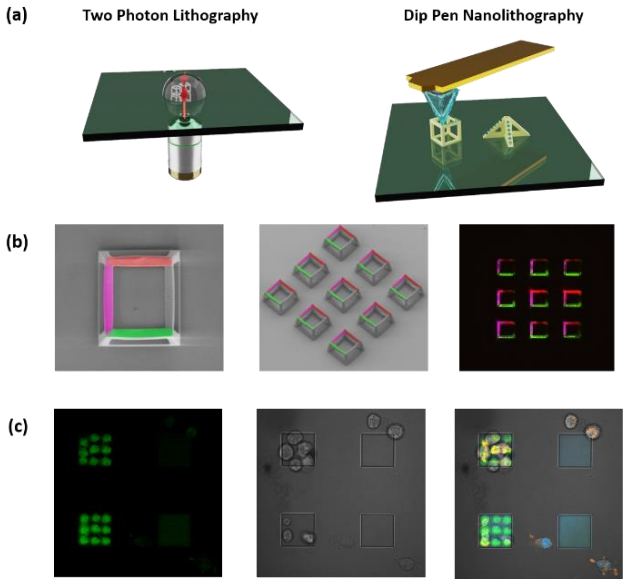

Figure 1. (a) The two techniques used to fabricate 3D cell scaffolds. (b) Polymeric scaffolds with different lipid inks selectively coating different parts of the structures. (c) Fibronectin spots patterned on squared-shaped scaffolds showing that they can selectively bind fibroblasts.

[1] J. L. Young, A. W. Holle, J. P. Spatz, Exp Cell Res 2016, 343, 3.

[2] G. Mathew, E. D. Lemma, D. Fontana, C. Zhong, A. Rainer, S. Sekula-Neuner, J. Aghassi-Hagmann, M. Hirtz, E. Berganza, Small 2024

[3] E. Berganza, M. P. Ebrahimkutty, S. Vasantham, C. Zhong, A. Wunsch, A. Navarrete, M. Galic, M. Hirtz, Nanoscale 2021, 13, 12642.

[4] J.A. L. Solaiman, C. Tavares, L. Martinez, A. Asenjo, E. Berganza, in preparation. (2025)