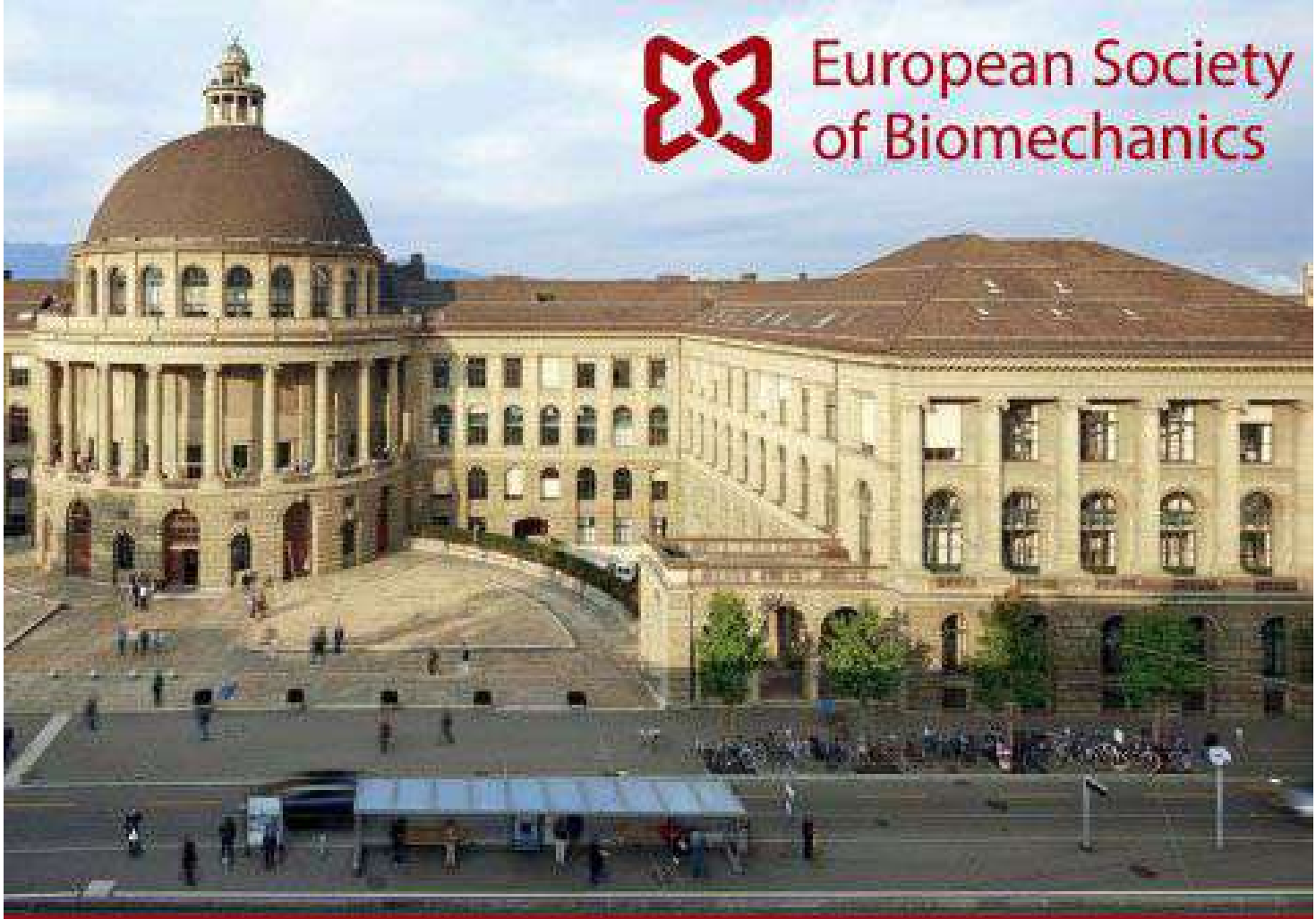

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INTEGRATING 3D MICROSCAFFOLDS ON POROUS MEMBRANES FOR CONTROLLED DRUG DELIVERY IN CAM ASSAYS

Leonardo Cherubin[1], Emanuele Mauri[1],Alessandra Nardini[1],Matteo Laganà[2],Rebeca Martinez[3],Giulio Cerullo[4],Roberto Osellame[3], Emanuela Jacchetti[1],Claudio Conci[1], Manuela T. Raimondi[1]

1. Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, P.zza L. da Vinci, 32, 20133 Milan, Italy. 2. Gemma Prototipi, Italy. 3Istituto di Fotonica e Nanotecnologie (IFN)-Consiglio Nazionale delle Ricerche (CNR), Milano, Italy, 4. Department of Physics, Politecnico di Milano, P.zza L. da Vinci, 32, 20133, Milan, Italy.

Introduction

Breast cancer chemotherapy treatment faces significant challenges due to the tumor microenvironment (TME) stiffening caused by fibrosis, which progressively impairs drug diffusion. The chorioallantoic membrane (CAM) assay can be a valuable model to address this problem. By implanting in the CAM several microscaffolds fabricated using two-photon polymerization (2PP) and seeded with breast cancer cells, we want to induce a fibrotic response that mimics the progressive diffusion barrier in a fibrotic TME. Once inserted in a flow chamber and interfaced to the CAM, the membrane permeability will enable in situ delivery of soluble factors, as anticancer drugs. In this work, we investigate the feasibility of fabricating microscaffolds on an implantable permeable membrane made of poly(dimethyl-siloxane) (PDMS). Additionally, we assess the diffusion and delivery of chemical species to the fibrotic TME models via the PDMS membrane, both experimentally and computationally.

Materials and Methods

We developed a 3D-printed flow chamber with a 200 µm-high channel, sealed between a 170µm-thick glass coverslip and a microstructured PDMS membrane (Fig. 1b-c). We microfabricated the membrane by first depositing a coating layer of poly(acrylic acid) (PAA) onto a previously plasma-cleaned 25-cm^2 Si-wafer via spin-coating (4000rpm, 30s), as to realize a 0.5-µm-thick "sacrificial layer". We deposited a 100-µm-thick PDMS layer by means of spin-coating (1000rpm, 30s). Subsequently, we fabricated a 2x2 array of pre-validated 3D microscaffolds (Fig. 1a) [1] (180x180x80µm^3) via 2PP. The resulting membrane was then immersed in dH_2O to facilitate its detachment from the wafer and that was sealed on the top of our millifluidic chamber. We designed and carried out computational fluid dynamics (CFD) and experimental tests on the flow chamber employing Rhodamine B as model drug.

Results

The PAA layer enabled an effective release of the PDMS membrane from the Si-wafer, essential for limiting stresses during the membrane transfer and therefore ensuring the stability of the microscaffolds. CFD simulations predicted that model drug administration with an inlet flow rate of 0.5mL/min and a concentration of 0.03mg/mL, allowed 2ng/min of model drug to diffuse through the PDMS membrane, reaching the CAM at the TME site (Fig. 1d). These results were calibrated through experimental data obtained from a custom-made test bench (Fig.1e), in which, under the a flow rate of 0.5mL/min, our model delivered 1.66ng/min ± 0.13 ng/min through the PDMS membrane, over a timeframe of 12-hours. The concentration of oxygen decreased by less than 10% across the PDMS membrane, from the fluidic channel to the CAM, ensuring minimal impact on oxygen availability at the site of the TME.

Discussion and Conclusion

If compared to conventional approaches [ref], our concept indicates a breakthrough in methods for targeted drug delivery in CAM assays. While previous studies administered anticancer drug broadly, topically or intravenously, resulting in diffuse and non-targeted effects, our method holds the potential to not only facilitate solutes distribution to the CAM, but also to enable control of drug administration to localized areas of interest, like the fibrotic TME developed here within the microscaffolds. Our concept will allow the discovery of new therapeutic approaches to contrast cancer, for example coupling chemotherapeutics to anti-fibrotics, and for refining drug administration protocols to improve therapeutic outcomes.

Figures

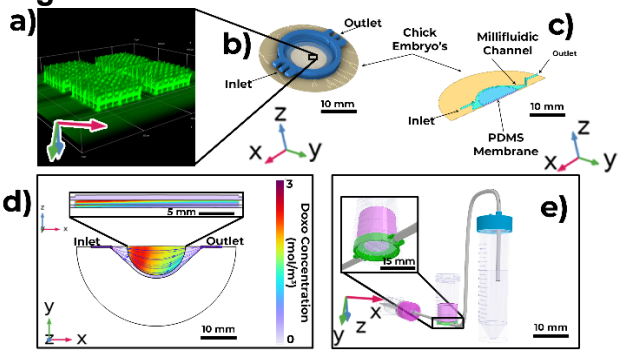

Figure 1: The concept. a)3D reconstruction of a 2x2 array of scaffolds from nonlinear microscopy images. b) FLow chamber to be interfaced to the CAM through the porous membrane. c)Geometry assumed for the CFD simulations. d)Prediction of Doxorubicin concentration mapped on the millifluidic chamber, the porous membrane and the CAM, 2 minutes after injection from the chamber inlet. e)Set-up for the experimental characterisation of drug diffusion through membrane.

References

1. Conci C et al., 10.1002/adom.202101103, 2022

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