Mapping transport properties of artificial 3D tissue viscoelastic microenvironments using on-chip hydrogel platforms

(collaboration between the DBE and the AMBER groups)

In their native microenvironment, cells interact with the surrounding insoluble extracellular matrix (ECM), with soluble components and with other cells in a dynamic and complex manner at different length and time scales. Artificial models that help us to study and understand such multiscale interactions in healthy and disease conditions will be valuable for the development of novel therapies and tissue engineering. **Some intriguing questions are how soluble components are transported through the ECM and if/how this process depends on the viscoelasticity of the ECM.** This could ultimately affect how soluble components are transported to and sensed by cells, which has potential implications for example, for nutrient availability, for tissue vascularization and for therapeutic drug delivery. Microfluidic platforms that allow the incorporation of hydrogels with tunable viscoelastic properties as ECM mimics, and offer dynamic culture conditions with perfusion and control on the flow of soluble components (e.g., concentration in a time- and concentration-dependent manner, flow rate) with enhanced mass transport, while enabling "continuous" imaging of cells and flows; are highly interesting to address above questions.

At the DBE, we have recently developed **dynamic covalent (DC) hydrogels that present tunable viscoelastic and stress-relaxing properties** and used them as artificial matrices for 3D cell culture [1]. Encapsulated cells showed high viability and increased metabolic activity when they were cultured in hydrogels of intermediate viscoelasticity. Building up on this work, we now want to investigate the effect of hydrogel's viscoelasticity on the transport properties of soluble components, as it has been recently reported that viscoelasticity can be used to control drug release [2]. We aim at studying transport process of soluble components of diverse sizes, across hydrogels of different viscoelasticity. For this purpose, we will apply an organ-on-chip model developed at AMBER, that **contains 3D engineered cellular models**, which can be fed with soluble components and their transport across the matrix be evaluated. We will monitor how transport and drug delivery can be affected by the material properties.

In this project, we will engineer 3D cellular models by encapsulating breast cancer cells, possibly in co-culture with fibroblasts, within a viscoelastic hydrogel and use it as a proof of concept for drug delivery, in the microfluidic platform. First, we will first study the transport of model soluble components across hydrogels of modulated viscoelasticity. We will check compounds delivery, cell uptake and cell metabolism in viscoleastic hydrogels. Additionally, oxygen concentration across the model will be mapped. Second, we will feed the engineered construct with a model chemotherapeutic drug and its cell uptake together with cell fate will be analyzed. We will study the effect of internal 3D viscoelasticity and fluid dynamics on cell survival, morphology, gene and/or protein expression and correlate this with the exact transport properties of the system. Ultimately, the results of this study are expected to facilitate the formulation of hydrogel-based new therapeutic treatments assisting in ECM remodeling to enhance drug delivery.

References:

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[3] C. Paggi, J. Hendricks, M. Karperien, S. Le Gac, *Lab Chip* 2022, 22 (9), 1815-1828.