Tumor viscoelasticity as a central player in glioblastoma treatment - towards mechanopharmacology

Viscoelasticity can be understood as the time-dependent response of the material to external mechanical stimuli. This means that the response to a stimulus is delayed, and there is a loss of energy inside the material. Living tissues, like a brain, are known to exhibit viscoelastic mechanical properties. Viscoelasticity of the brain tissue plays a critical role in tissue homeostasis and can be altered due to pathological processes, like cancer development. To study the role of tissue viscoelasticity, hydrogel systems that mimic the mechanical properties of the tissues are developed and used as substrates for cell culture. Growing cells on such substrates allows to understand cellular responses to viscoelasticity, like cell spreading, proliferation, migration, and differentiation.

The latest data shows nearly 90% of clinical drug development worldwide fails. One of the possible reasons is that the screening and preclinical pharmacology are established in cell culture with an oversimplified mechanical environment. The widespread study of mechanobiology gave rise to novel *in vitro* systems, from 2D to 3D environments, with viscoelastic properties resembling those of biological tissues. Still, most *in vitro* cell culture substrates are purely elastic soft hydrogels that do not account for the viscosity of biological tissues. With this project, we propose to understand the role of viscoelasticity in normal and cancer brain cell function and their response to anticancer drugs. This biomechanical approach will be accompanied by a set of transcriptome profiling experiments for brain cancer cells using next-generation RNA sequencing (RNA-seq) to detect differentially expressed genes between cancerous cells grown and treated on elastic or viscoelastic matrices. *In vitro* data will be correlated with patient-derived cells and animal model of brain cancer.

During project realization, we will explore the possibility that tissue viscoelasticity controls not only cancer development and growth but also single cancer cell response to anticancer treatment. Therefore, the scientific goal of the project is to employ biomechanically appropriate *in vitro* systems to study the pharmacological responsiveness of human brain cancer cells and identify key genetic factors that are related to viscoelasticity-sensing and contribute to treatment failure.