Tissue engineering aims at fabrication of 'artificial' tissues, that is engineered constructs involving living cells and performing the native tissue functions, yet outside the body. Such engineered tissues offer multitude of applications including (i) tissue regeneration, where they could be used directly as implants to replace damaged tissues, (ii) basic tissue biology research, offering highly controlled experimental conditions—unlike those encountered in vivo—allowing insight into specific physiological phenomena, and (iii) testing of drugs—both in pharmaceutical industry, as an alternative to animal models—and in personalized medicine, e.g., in cancer treatment. A fundamental problem in tissue engineering is fabrication of tissues with an embedded vasculature which allows circulation of nutrients and sustains long-term viability. In particular, the vasculature must be functional at all relevant length scales, down to the cellular scale where smallest vessels, built of endothelial cells (EC), are to deliver oxygen and remove metabolic byproducts directly from individual cells. Current approaches to vascular tissue engineering typically rely on spontaneous self-assembly of the endothelial cells into branched tubular networks. However, such self-assembled networks are far from optimal since (i) they develop slowly in time as the cells need to migrate through hydrogel over relatively large distances, (ii) they are heterogeneous and weakly percolated, and (iii) they do not allow any external control over their global structure.

In the project we will develop a new method of vascular tissue engineering based on the use of so-called vascular 'seeds', that is pre-aggregated clusters of endothelial cells which—when distributed inside a host tissue in controlled manner—could guide the formation of vascular networks of pre-designed global architecture. In the project we will study formation of vascular networks 'sprouting' from multiple seeds dispersed in an external hydrogel mimicking the host extracellular matrix. To control the spacing between the seeds we will order them into arrays using magnetic forces and confine inside a planar transparent chamber allowing direct imaging of the forming vascular networks. To characterize the networks we will develop cutting-edge image analysis tools based, i.a., on machine learning, as well as provide a detailed theoretical model of the developing network incorporating, for the first time, direct interaction of the endothelial cells with the surrounding extracellular matrix. We will use the model to design optimal networks that could most efficiently support the engineered tissues.

Finally, we will co-culture the vascular networks with cancer cells as a realistic in vitro model of the cancer tissue. It is well known that angiogenesis plays a key role in cancer development, invasion, and metastasis. Solid tumors, e.g., lymphomas, sarcomas as well as cancers of breast, prostate or thyroid, need a blood supply if they are to grow beyond a few millimeters in size. Therefore cancer vasculature has been targeted in cancer therapies as well as used to deliver drugs directly to cancer cells. We will use our platform to test drugs on several different cancer cell lines (e.g., of breast cancer) to develop tools for future use in personalized approaches in which the diseased cells could be harvested directly from a patient to develop an optimal patient-specific treatment strategy.

In summary, the project will significantly advance the field of vascular tissue engineering, deliver new data analysis tools for general angiogenesis research, provide data-driven predictive theoretical models of developing vascular networks, as well as open new perspectives in development of miniaturized platforms for drug testing, e.g., applicable in personalized cancer therapies.