Universität Basel

# Research Project

# Decoding the molecular regulation of intussusceptive angiogenesis for therapeutic targeting

## Third-party funded project

**Project title** Decoding the molecular regulation of intussusceptive angiogenesis for therapeutic targeting
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**Department**
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Background. Ischemic cardiovascular disease is the most common cause of death in the Western world and, despite advances in medical and surgical therapy, the morbidity and mortality remain very high. Therapeutic angiogenesis aims to induce the formation of new blood vessels to improve the perfusion of ischemic tissue in patients with end-stage coronary artery or peripheral arterial disease that are not amenable to other treatment options. Vascular Endothelial Growth Factor-A (VEGF) is the master regulator of vascular growth and it has been tested clinically with a variety of delivery methods. However, the results of placebo-controlled clinical trials have been disappointing and yielded mostly negative results. Retrospective analyses showed that the effects of VEGF can be deleterious if uncontrolled, and achieving therapeutic efficacy with VEGF gene delivery at safe vector doses has proven particularly challenging, despite the exquisite biological potency of the factor. Therefore, there is a clear need to better understand the molecular and cellular mechanisms regulating vascular growth under therapeutically relevant conditions of VEGF delivery.

Rationale. We previously found that VEGF induces normal or aberrant angiogenesis depending on its concentration in the microenvironment around each producing cell in vivo, rather than on the total delivered dose. Our results in the previous funding period show that: 1) VEGF delivery to skeletal muscle at therapeutically relevant doses induces angiogenesis by the mechanism of intussusception rather than by the well-studied process of sprouting; and 2) the regulation of VEGF-induced intussusceptive angiogenesis is likely fundamentally different from that of sprouting, with divergent therapeutic consequences. Yet, the molecular mechanisms of intussusception remain poorly understood compared to the regulation of sprouting, mainly due to a paucity of appropriate models.

Specific aims. Here we propose to systematically investigate the molecular regulation of intussusceptive angiogenesis in skeletal muscle (the tissue affected by peripheral artery disease) under therapeutically relevant conditions of angiogenic factor delivery. Specifically, we aim to: 1) establish a platform for high-resolution *in vivo* imaging of intussusceptive angiogenesis in skeletal muscle by 2-photon microscopy; 2) systematically investigate its molecular regulation by a stage-specific and VEGF dose-dependent unbiased analysis of the vascular transcriptome; and 3) elucidate the function of the identified signaling pathways by loss-of-function and gain-of-function experiments.

Experimental design. Monoclonal populations of retrovirally transduced myoblast, which homogeneously secrete different amounts of VEGF, or a highly controlled fibrin-based platform for protein delivery, will be used to deliver specific VEGF doses in skeletal muscle.

Expected value of the proposed project. The experiments proposed are expected to provide much-needed fundamental insight into the mechanisms of therapeutic intussusception, as well as a rational basis for the design of future treatment strategies.

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**Add publication**

**Add documents**

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