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Therapy of cancer *via* the follicle-stimulating hormone receptor, a marker of peripheral tumor vasculature

Improved molecular understanding of human cancer has resulted in identification of various cancer cell targets for therapeutic interventions. Unfortunately, tumor heterogeneity hampers tumor-specific targeting. The problem of tumor heterogeneity is supposed to be reduced by targeting the tumor-associated vasculature. The latter, a ubiquitous component of cancer, is essential for tumor growth and metastasis. Therefore, depriving a tumor from its oxygen and nutrients, either by preventing the formation of new vessels (angiogenesis), or by disrupting vessels already present in the core of tumors (“anti-vascular therapy”), appears to be an effective treatment modality in oncology. (Vascular targeting agents for the treatment of cancer are designed to cause a rapid and selective shutdown of the blood vessels of tumors.)

However, the efficacy of these therapies is substantially compromised by the inability of drugs to completely kill tumor cells located at the periphery of the tumor mass. Therefore, the future of anti-vascular cancer therapy may depend on finding new targets on peripheral vessels that make connections between the normal blood circulatory system and the tumor core blood vessels. The presence of specific endothelial cell markers exposed on the luminal surface of tumor peripheral vessels may offer an opportunity for marker-specific delivery of vessel-disrupting drugs (Figure 1).

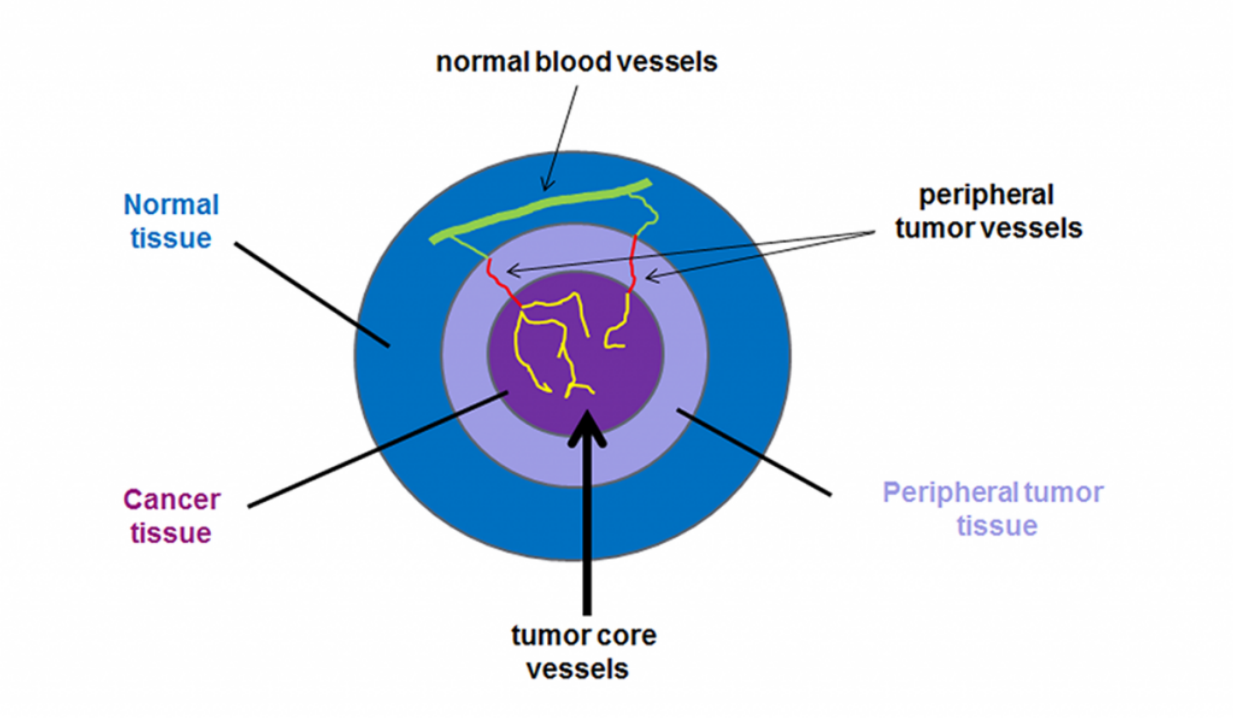

Figure1: Distroying the tumor peripheral blood vessels (drawn in red) could by an effective treatment in oncology

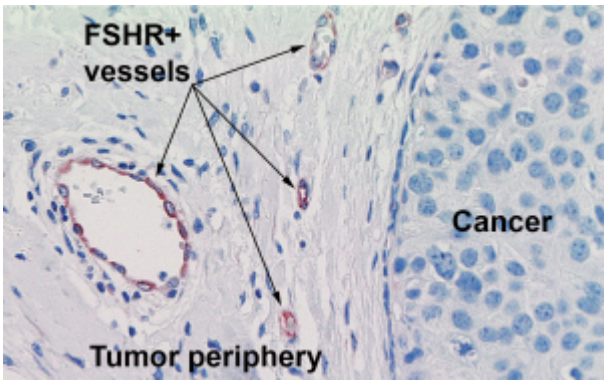

Figure 2: blood vessels at tumor periphery epxress FSHR

We have obtained evidence that this is the case for FSHR, a G-protein linked receptor that binds FSH, a key hormone in mammalian reproduction. FSHR was shown to be expressed selectively on the luminal surface of tumor blood vessels. A general characteristic of the blood vessels that express the endothelial FSHR is that they are located at the periphery of the tumors (Figure 2). We have also noticed that tumors generated in nude mice following subcutaneous injection of a human prostate cancer cell line reveal strong staining of FSHR in the tumor peripheral blood vessels. In this model we showed also that a nanoparticulate FSHR-ligand is internalized into the tumor endothelial cells.

This observation confirms the feasibility of anti-vascular therapy by agents that require binding and internalization, like FSHR ligand-toxin conjugates.

We propose to synthesize anti-vascular therapeutic agents and to verify their efficacy in preclinical cancer models. The agents will contain a targeting component linked to a cell-toxic component. The targeting moiety consists in a highly specific anti-FSHR monoclonal antibody. The targeting component consists in a plant toxin and/or a cytotoxic drug. The components will be joined by covalent coupling or as a chimeric protein. The ability of the agents to bind to the target and to induce cell death will be tested in endothelial cell cultures that express FSHR. Subsequently the agents will be tested in nude mice that carry xenograft human breast tumors, ovarian cancer, and colon cancer.

We will also investigate the effects of the agents that can block the endothelial FSH/FSHR signaling on the tumor vessels, their efficacy of inhibiting tumor growth as well as the lack of adverse effects on normal tissues.