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EDITORIAL – TRANSLATIONAL RESEARCH AND BIOMARKERS

Editorial: A Novel Monoclonal Antibody-Targeting Angiogenesis by Inhibiting Secreted Frizzled-Related Protein 2

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The legendary surgeon-scientist Judah Folkman contributed a wealth of discoveries on the fundamental role of angiogenesis in cancer and other diseases.[1] This line of investigation led to more than 50 angiogenesis inhibitors being investigated in clinical trials and at least 10 that are currently approved by the US FDA.[2] Angiogenesis inhibitors work via a variety of mechanisms of action. Some specifically bind to (1) vascular endothelial growth factor (VEGF) or its receptor; (2) other growth factors such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF); or (3) receptors or proteins on endothelial cells, blocking the growth of blood vessels.[3,4] Angiogenesis inhibitors remain an attractive topic for preclinical development for cancer therapy.

Secreted frizzled-related protein 2 (SFRP2) is a modulator of Wnt signaling that is expressed in the vascular endothelium of the majority of solid tumors.[5] Courtwright et al. reported that SFRP2 mediates angiogenesis by demonstrating that tacrolimus inhibition of SFRP2 decreased vascular tube formation in vitro and reduced the growth of angiosarcoma xenografts in vivo.[5] Garcia et al. build upon this work in the article entitled "Development of a novel humanized monoclonal antibody to secreted frizzled-related protein-2 that inhibits metaplastic breast cancer and angiosarcoma growth in vivo".[6]

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This study focuses attention to SFRP2 inhibition in angiosarcomas and triple-negative breast cancer, two aggressive malignancies where there exists an unmet need for targeted therapies directed at tumor biology. Targeted therapy efficacy is improved when biomarkers can be found that help identify a responding patient population. It is encouraging that SFRP2 does appear to be strongly expressed in around 70% of breast cancers as well as many other types of cancers based on a query of The Human Protein Atlas (www.proteinatlas.org).[7] The authors have found that SFRP2 is broadly expressed across a variety of solid malignancies, both epithelial and mesenchymal in origin. Specifically, high SFRP2 expression is seen in 85% of triple-negative breast cancers and 100% of angiosarcomas.[5] Other investigators have also shown that the family of SFRPs appears to play an important role in osteosarcoma.[8] Importantly, SFRP2 and its related isoforms are involved in the Wnt pathway, which plays a critical role for many other sarcoma subtypes (e.g. desmoid tumors, synovial sarcoma),[9–11] which suggests potentially even more relevance for this particular group of malignancies.

The authors elegantly demonstrated that their humanized monoclonal antibody against SFRP2 reduced tumor growth and increased apoptosis of SVR angiosarcomas and Hs578T triple-negative breast cancers in vivo. There is definitely a need to demonstrate preclinical efficacy in mice prior to human clinical trials, but the immunodeficient mouse model and the lack of immune response when tested in vitro with healthy human blood argues against the mechanism of action being related to the host immune response. This could be further studied using immunocompetent syngeneic mouse models such as 4T1 in BALB/c mice to model triple-negative breast cancer. Alternatively, genetically engineered mouse models such as FVB-

Tg(C3-1-TAg) or the p53 null 'T11' models for triple-negative breast cancer or the Pdgfrb-Cre, $Trp53^{R172H/R172H}$ and H2 K-fos-tg mouse models for angiosarcoma and osteosarcoma, respectively, could be used.[12–15] These models would need to be tested to see if they express the human target antigen, or otherwise engineered to do so.[16]

Immunotherapy has become a widely used modality in many advanced cancers. The concept of synergy between angiogenesis inhibitors and immunotherapy is of great interest and has been explored by several other groups.[17,18] Vascular normalization could, in theory, lead to a more effective influx of immune cells necessary to achieve an antitumor response.[19] Furthermore, the hypothesis that immune checkpoint inhibitors could improve the efficacy of antiangiogenic therapies in cancer is certainly deserving of further investigation.[12,20,21] Immunotherapies can inhibit the immunosuppressive endothelial barrier via inhibition of programmed death-1 (PD-1) activation.[20] Endothelial programmed death-ligand 1 (PD-L1) expression has been reported to regulate angiogenesis by directly modulating VEGF receptor 2 (VEGFR2) expression and increasing endothelial proliferation; therefore, PD-1 blockade could have antivascular activity.[22] This mechanism is in line with emerging evidence that angiogenesis and immunosuppressive responses frequently occur simultaneously physiologically but may be capitalized on by malignancies.[23]

Antagonism of SFRP2 in the vascular endothelium would be expected to inhibit tumor growth, angiogenesis, and tumor migration. Accompanying these expected therapeutic effects would be toxicities. Serious toxicities seen with antiangiogenic therapeutics, such as VEGF inhibitors and multitargeted tyrosine kinase inhibitors, include hypertension, hemorrhage, thrombosis, stroke and/or myocardial infarction, proteinuria, reversible posterior leukoencephalopathy, and endocrine dysfunction.[24–26] Impaired wound healing via inhibition of migration and proliferation of endothelial cells is also an important described adverse effect. Therapy utilizing monoclonal antibodies have described infusion-related reactions to varying degrees.[27] Although experience with bevacizumab (a humanized monoclonal antibody to VEGF) has not demonstrated clinically significant hypersensitivity,[28] the potential for infusion-related reactions with this novel agent should not be ignored. Finally, other described adverse effects include fatigue, gastrointestinal symptoms, hand–foot syndrome, stomatitis, cutaneous toxicity, and hepatotoxicity.

Looking to the history of VEGF inhibition and other angiogenesis inhibitors, clinical benefit has been described with monotherapy of a few agents (e.g. cabozantinib, ramucirumab, sunitinib, sorafenib), and, more significantly, in combination with cytotoxic chemotherapy in a wide range of solid tumors.[24,25,29] Therefore, determining the efficacy of preclinical and eventually clinical combinations with cytotoxic chemotherapy and even immunotherapy will be useful future strategies.[29] Important directions moving forward will be to understand mechanisms of resistance to SFRP2 inhibition and examine the role of SRFP2 inhibition in combination with other modalities of therapy (i.e. chemotherapy, radiation, immunotherapy, and other targeted therapies).

Garcia et al. are to be congratulated on optimizing and developing a novel experimental therapeutic agent; however, much work still remains to be done before embarking on clinical trials. Preclinical studies such as pharmacokinetics (PK), toxicokinetics (TK), serum concentrations of treated animals, tissue cross-reactivity, local tolerance, as well as single and repeat dose toxicity must be considered prior to applying to the US FDA for an Investigational New Drug (IND) application.[30] It is customary that phase I trials include a large spectrum of solid malignancies, including patient populations suitable for treatment with a goal of determining the recommended phase II dose (RP2D) and establishing the safety of the drug in humans. It would be anticipated that the target populations of interest, angiosarcoma and triple-negative breast cancer patients, would be well represented in a phase II trial, in which a preliminary efficacy signal might be detected. The process of drug discovery is an arduous one, but the timeline for clinical trial testing of a novel cancer therapy may take an additional decade. Given that patients with often lethal cancers such as angiosarcomas and triple-negative breast cancers may stand to benefit from this novel therapy, we encourage the authors to go full speed ahead to embark on clinical trials evaluating this monoclonal antibody.

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