



# An antivascular vaccine to boost self-immunity and strike the tumor

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Vascular endothelial growth factor (VEGF) family members and their receptors have long been considered suitable anticancer targets (1) because of their role in angiogenesis. Although their full potential remains to be realized, two monoclonal antibodies have been Food and Drug Administration-approved against human cancer: bevacizumab (humanized anti-VEGFA) and ramucirumab (fully human anti-VEGFR2). In PNAS, Wentink et al. (2) describe the rational engineering of 3D-structured peptides that mimic the bevacizumab binding site of VEGFA, thereby eliciting a strong immunogenic response in rats. The resulting sera proved at least as efficient as bevacizumab itself in inhibiting tumor xenografts in immunodeficient mice. Active immunization of immunocompetent mice bearing syngeneic tumors was somewhat effective, but limited by: (i) high mortality upon serial epitope administrations, presumably from anaphylaxis; (ii) need of repeated vaccinations and incomplete tumor control; and (iii) increased serum VEGF levels. These results raise corresponding concerns: (i) the anaphylactic response seems related to the epitope itself, which casts doubt for translational applications; (ii) it is unlikely that a sufficient response could be reached in humans to effectively control tumor growth; and (iii) the presence of antibody:VEGF complexes with decreased clearance rate has to be discriminated from an actual increase in free VEGF, which could impact on tumor angiogenesis/metastasis.

Despite such technical limitations, which are inherent in an initial report, the Wentink et al. study (2) provides interesting insights. It is well-known that tumors induce an immunosuppressive microenvironment by influencing tumor infiltration by dendritic cells and T-regulatory cells (3), a phenomenon mediated—at least in part—by VEGF family members (4). Therefore, a therapeutic approach targeted

to VEGFA would likely contribute to release such immunosuppression, besides interfering with pathological angiogenesis. Interestingly, a comparable release of tumor immunosuppression has been observed in rare cases of spontaneous cancer regression that occur following surgical removal of the primary tumor, radiofrequency ablation, and ionizing radiation-based treatments. Self-vaccination against tumor epitopes has been invoked as a possible explanation for such abscopal effect, which has long been recognized in metastatic renal cell carcinoma (RCC), among a few other tumor types (5).

In this context, we have designed an antibody fingerprinting technology to identify tumor-directed antibodies in sera from patients. Such a high-throughput approach proved effective in the identification of autoantibody signatures in prostate and ovarian cancer (6–8). In ongoing work, we have applied this protocol to sera from an index patient with well-documented spontaneously regressed metastatic RCC (9), as well as to a classic experimental rat model of RCC (10), corroborating the presence of a humoral immunity against the broad repertoire of tumor vascular antigens. Because Wentink et al. (2) show that an immune response against VEGFA can induce preclinical antitumor vaccination, we believe that a patient-tailored version of this approach (including other members of the VEGF ligand-receptor family) could potentially be used to boost an acquired immune response to strike the tumor. Thus, evaluation of autoantibody pools against endothelial epitope combinations to potentially achieve a comprehensive immune effect would be a logical preliminary step. Together, these findings may provide the basis for translation applications of Wentink et al. (2).

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2 Wentink MQ, et al. (2016) Targeted vaccination against the bevacizumab binding site on VEGF using 3D-structured peptides elicits efficient antitumor activity. *Proc Natl Acad Sci USA* 113:12532–12537.

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