with this multipeptide immune response. The role of Treg cells in T-cell–mediated immunotherapy, were correlated with cyclophosphamide, which inhibits Treg cells. As in the case of IMA901 in combination with a single-dose pretreatment in 68 patients with metastatic RCC were given IMA901 to improve clinical outcome. In addition, pretreatment analysis of cellular and serum biomarkers identified 2 subgroups of myeloid-derived suppressor cells and the proteins APOA1 and CCL17 as predictors of immune responses and increased overall survival in RCC. These results suggest that rational antigen discovery and validation, combined with monitoring of T-cell responses and biomarkers, may enable the development of effective cancer vaccines.

**PROAPOPTOTIC DEATH RECEPTOR AGONISTS ACT AS VASCULAR DISRUPTING AGENTS**

Agonistic antibodies and recombinant ligands targeting cancer cells that express proapoptotic death receptors 4 and 5 (DR4/5) have been evaluated in clinical trials but have had limited success. Preclinical studies with these agents, which frequently do not activate murine death receptors, have mainly been performed on cultured cells or human tumor xenografts and thus have not evaluated the effects of death receptor activation on the tumor microenvironment. Wilson and colleagues therefore evaluated the effects of an oligomeric form of TRAIL (also called Apo2L), capable of engaging murine DR5, on murine tumors. Within 24 hours of treatment, severe disruption of the tumor vasculature occurred, leading to extensive tumor hemorrhage and widespread tumor cell death. Surprisingly, these effects were dependent on DR5 expression in endothelial cells in the stroma of tumor-bearing mice, as oligomeric TRAIL had no effect in DR5-deficient mice. Oligomeric TRAIL rapidly and selectively induced apoptosis in tumor-associated endothelial cells, regardless of DR5 expression in the tumor cells. Endothelial DR5 activation led to decreases in tumor vascular density and increased vascular permeability, causing hemorrhagic tumor necrosis and reducing tumor growth. To determine whether these findings might be relevant in human cancers, the authors analyzed DR5 expression in a panel of 43 primary human non–small cell lung cancers and found that approximately 10% of the samples had regions of DR5 expression in the tumor endothelium. Because the authors did not observe DR5 expression in normal endothelium or in most other human tissues, these findings suggest that proapoptotic death receptor agonists may potentially be safely and effectively repurposed as vascular disrupting agents for anticaner therapy.


**VACCINE-SPECIFIC IMMUNE RESPONSES CORRELATE WITH CLINICAL BENEFIT**

The efficacy of cancer vaccines depends on the identification of tumor antigens that elicit a successful immune response. Walter and colleagues used an antigen discovery platform to generate the IMA901 vaccine, which is composed of multiple tumor-associated peptides (TUMAP) that were validated as naturally presented, overexpressed cancer antigens. This vaccine was then tested in clinical trials for the treatment of advanced renal cell cancer (RCC). In a phase I trial of 28 patients, the IMA901 vaccine was well tolerated and induced T-cell responses in 20 patients, as measured by in vitro detection of TUMAP antigen-specific T cells. Retrospective analysis showed that response to multiple TUMAPs led to an increase in disease control and that lower prevaccine numbers of regulatory T (Treg) cells, which suppress T-cell–mediated immunotherapy, were correlated with this multipeptide immune response. The role of Treg cells was further evaluated in a subsequent phase II study, in which 68 patients with metastatic RCC were given IMA901 or IMA901 in combination with a single-dose pretreatment of cyclophosphamide, which inhibits Treg cells. As in the phase I trial, there was a high immune response rate, and the response to multiple TUMAPs extended patient survival time. Moreover, treatment with cyclophosphamide was associated with a prolonged median overall survival, particularly among immune responders, in which cyclophosphamide treatment led to a reduction in proliferating Treg cells, suggesting that cyclophosphamide enhances the antitumor benefit of vaccine-induced immune responses. In addition, pretreatment analysis of cellular and serum biomarkers identified 2 subgroups of myeloid-derived suppressor cells and the proteins APOA1 and CCL17 as predictors of immune responses and increased overall survival in RCC. These results suggest that rational antigen discovery and validation, combined with monitoring of T-cell responses and biomarkers, may enable the development of effective cancer vaccines.
