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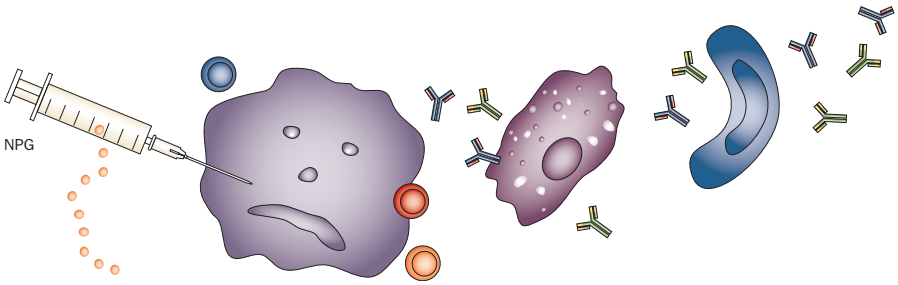
IMMUNOTHERAPY

Harmonizing the immune response with a cancer vaccine



Some cancer vaccines with a reasonable safety profile have demonstrated efficacy, but the holy grail of vaccine therapy is to identify the appropriate tumour antigens to target, as well as overcoming the host immune regulatory mechanisms that oppose immunotherapy. Importantly, predictive biomarkers to help improve our understanding of patient responses to vaccine therapy remain elusive. Now, a pivotal study by Steffen Walter, Toni Weinschenk and coauthors published in *Nature Medicine* has shown that a multipeptide vaccine given after a single dose of cyclophosphamide can prolong survival in patients with renal-cell cancer (RCC). This study also identified putative predictive biomarkers of immune response and clinical benefit to the vaccine.

Harpreet Singh-Jasuja, senior researcher of the study, describes the background work that led to the research findings, "we had started working on identifying naturally presented multiple tumour-associated peptides (TUMAPs) in RCC in the late 1990s at the University of Tübingen, in the group led by Hans-Georg Rammensee. This work provided two key observations. First, it was possible to identify, select and validate TUMAPs using a combination of mass spectrometry, transcriptomics and immunology. Second, when patients with RCC were vaccinated with peptides (loaded onto dendritic cells), we could observe encouraging immune responses and some indication of clinical activity in a small phase I trial." These findings led Singh-Jasuja and his team to hypothesize that the use of a larger number of TUMAPs might overcome tumour escape mechanisms and, therefore, result in a better clinical benefit.

The current study describes approximately 8 years of development spanning from early discovery to results from a randomized phase II study that culminated in the design and initiation of an ongoing phase III trial. Initially, Singh-Jasuja and colleagues used the XPRESIDENT antigen discovery platform to identify, select and validate naturally presented TUMAPs and create a multipeptide vaccine using a combination of mass spectrometry (peptidomics), transcriptomics, immunology and bioinformatics. The safety and immunogenicity of the IMA901 vaccine was tested in 28 patients with advanced-stage RCC in a phase I trial; the efficacy of the vaccine was then further assessed in 68 patients in a phase II trial. By measuring regulatory T cells (T_{regs}) prior to vaccination, the researchers observed that high levels of T_{regs} were negatively associated with immune responses. They then tested in a randomized fashion whether single-dose cyclophosphamide pretreatment could reduce the numbers of T_{regs} and enhance the response.

Singh-Jasuja explains, "we confirmed that single-dose cyclophosphamide reduced T_{regs}, which is the first time this has been established in a randomized clinical trial." Using a prospectively designed analysis, the investigators showed that patients pretreated with cyclophosphamide and who responded to the vaccine had a prolonged survival—an observation not seen in vaccinated patients without the pretreatment. No survival difference was observed among nonresponders to the vaccine, indicating that single-dose cyclophosphamide lacks intrinsic antitumour activity, but is an immunomodulator that synergizes with the vaccine to provide clinical benefit. Singh-Jasuja continues, "we went on to show that two types of myeloid-derived suppressor cells (MDSC) are negatively associated with survival of RCC patients. Thus, these data provided the rationale to combine IMA901 with sunitinib—the first-line standard of care in RCC, which is known to reduce the number of MDSC. This combination is currently being tested in a randomized, controlled phase III trial, whereby sunitinib plus IMA901 is being compared with sunitinib alone."

To extend these findings further, Singh-Jasuja's team used various established assays based on ELISA methodology to detect serum biomarkers to identify predictive markers associated with immune response and patient survival. Serum concentrations of two markers, apolipoprotein A1 and CCL17, were positively predictive of patients who had a significantly longer overall survival. Crucially, as Singh-Jasuja points out, "this is the first study to identify putative predictive biomarkers for immune response and clinical benefit to a vaccine." There are several implications for the field of cancer immunotherapy: "foremost that it seems to be highly relevant to support the *in vivo* activity of cancer vaccines by using appropriate immunomodulators (such as cyclophosphamide), and to implement a comprehensive biomarker programme as guidance for cancer vaccine development."

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Original article Walter, S. *et al.* Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. *Nat. Med.* doi:10.1038/nm.2883