EDITORIAL

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Immunotherapy: combine and conquer

Recent clinical data suggest that combination immunotherapy may be the wave of the future. To capitalize on these exciting findings, the scientific, logistical, proprietary and financial hurdles to the clinical testing of combination therapy must be addressed.

Crowned *Science* magazine's 'Breakthrough of the Year' in 2013, cancer immunotherapy has shown no sign of slowing down in terms of the level of excitement it incites in clinicians, patients, researchers or scientific journals. Recent clinical results with engineered T cell therapy and checkpoint blockade have been so remarkable as to elicit from some the word 'cure' in the same sentence as 'cancer'. In light of the therapeutic responses of unprecedented durability that have been reported, a major question in the field is how to broaden these responses to more patients with a wider variety of malignancies.

Recent phase 1 trials of the combination of the checkpoint inhibitors anti–PD-1 and anti–CTLA-4 point the field in one major direction: combination therapy. In a cross-comparison of trials, the clinical response rate of the inhibitor combination was higher than that of either monotherapy.

The potential range of drug combinations extends far beyond anti–PD-1 and anti–CTLA-4, and includes additional checkpoint inhibitors such as those targeting OX40, GITR, TIM-3 and LAG-3. It reaches beyond checkpoint inhibitors to cancer vaccines, engineered T cells, radiotherapy, and small molecules targeting oncogenic drivers. The number of different potential combinations of therapeutic approaches and tumor types is staggering. So it is arguably a good time to examine what steps are needed to streamline the translation of combination immunotherapies.

One step is to rationally identify different monotherapies from among the long menu of options, and to pair them with the malignancies that are most likely to respond. Strong preclinical data can help in this regard: the enhanced effect of anti–CTLA-4 and anti–PD-1, compared to either therapy alone, was anticipated on the basis of preclinical data revealing that these agents target non-redundant T cell checkpoint pathways. Of course, it is not guaranteed that combinations that work in mice will work in humans; no mouse model of cancer perfectly recapitulates human disease, as discussed in a Perspective in this issue (page 431). An example particularly relevant to immunotherapy is the fact that many mouse tumors do not harbor a high number of mutations, but high mutational burden seems to correlate with therapeutic response to anti–CTLA-4 and anti–PD-1 in patients.

A second step is to better select those patients who are likely to respond. Although in theory immune responses can be elicited against any tumor, the reality is that the responses in unsorted patient populations are still limited, and more pronounced in some tumor types than in others. Understanding which immune mechanisms are active in tumors at different stages of disease will be essential for selecting monotherapies to combine in various orders in different patients. Clinical trials designed to acquire correlative cellular and molecular data that inform the quality and evolution of the immune response may provide such mechanistic data and reveal biomarkers that can better tailor combinations to individual patients.

Studies of patients treated with anti-CTLA and/or anti–PD-1 have already yielded potential biomarkers of response, but reveal a more complex dynamic than the arguably more linear relationships between tumor cell molecular targets and their drugs. For instance, in some trials, responses to PD-1–targeting agents correlate with the level of PD-1's ligand PD-L1 on tumor-infiltrating immune cells or on tumor cells. Also, as mentioned above, the neoantigen profile of tumors from melanoma patients treated with CTLA-4 blockade suggests that a specific mutational signature is associated with response. Larger randomized trials will be needed to validate the predictive power of the potential biomarkers. As biomarkers may not be static serial biopsies—preferably of blood—may be required to assess the evolution of tumor and immune responses over the course of therapy, as well as to dynamically adjust treatment in a personalized manner.

In addition to scientific issues, logistical, proprietary and funding hurdles can limit the combinatorial strategies that will be available for testing (*Nat. Med.* **21**, 105, 2015). Notably, some nonprofit organizations are stepping up to address these issues. On 20 April, Stand Up To Cancer and the American Cancer Society announced funding of up to $20 million to a Lung Cancer Dream Team that will, among other research goals, integrate targeted therapies with immunotherapies. Another organization, Cancer Research Institute (CRI) has collaborated with Ludwig Cancer Research to take a more systematic approach to enabling testing of combination therapies. Launched in 2012, their Clinical Accelerator assembled a network of 60 leading academic immunotherapy researchers who select innovative combinations on the basis of preclinical and other data. Then, CRI and Ludwig negotiate with the biopharma companies that are developing these therapies and provide nonprofit funds and clinical trial management expertise in exchange for the rights to include these therapeutic agents in clinical trials that are designed and run by CRI and Ludwig experts. These trials are designed for the dual purpose of testing efficacy and harvesting mechanistic insights that will help select future drug combinations and identify biomarkers of response. So far, 11 announced company partners are providing access to more than 30 drugs speaking to the success of this effort. However, considering the multitude of possible combinations of therapeutic agents, immune pathways and malignancies, additional efforts will be needed and should be encouraged.

Immunothereapy has the potential to change the course of cancer treatment and may offer the long-elusive possibility of a cure for some types of cancer. But a collaborative and integrative approach will be the key to maximizing the impact of the field as a whole. Integrating findings in basic tumor biology and tumor immunology may hold the potential for a two-pronged approach to further increase rates of response. Concerted efforts between scientists, companies, funders and advocacy organizations are needed to fill a rational pipeline that prioritizes the best combinations for each tumor context, streamlines patient selection and response monitoring, and ensures that the word 'cure' is uttered more and more frequently.