Uncoupling Toxicity from Therapeutic Efficacy: The New Challenge of Immunotherapies

Commentary by Alessia Armezzani, PhD, & Amélie Rezza, PhD 13/04/2021

The emergence of immuno-oncology and, more specifically, checkpoint inhibitors have represented a ray of hope in the fight against cancer, offering the prospect of remission to patients suffering from diseases whose outcomes were previously invariably terminal. Among the most promising drugs is a monoclonal antibody targeting CTLA-4—ipilimumab—which has been the first checkpoint inhibitor to be tested and approved for the treatment of late-stage metastatic melanoma.[1] It has been since shown that combination therapy targeting checkpoint inhibitors CTLA-4 and PD-1, such as ipilimumab and nivolumab, is even more effective than monotherapy that targets CTLA-4 alone. Indeed, the combined use of both these antibodies can greatly improve the outcome of patients affected by many types of cancers, including metastatic melanoma, renal cell carcinoma, colorectal cancer, and small cell lung cancer, compared to ipilimumab alone.[2–4] Similar clinical benefits have been observed with a different CTLA-4/PD-1 combination therapy—tremelimumab and durvalumab—confirming that the combined use of checkpoint inhibitors represents a promising and efficient treatment for a broad range of tumors.[5]

Despite their clear potential, it is now broadly acknowledged that checkpoint inhibitors display a major limitation: the onset of immune-related adverse effects (irAEs). In layman's terms, targeting the immune system to fight cancer cells can induce collateral damage in healthy organs, which poses a real dilemma. Therapies targeting CTLA-4, the "king" of immune checkpoint, perfectly illustrate this conundrum. CTLA-4 is known to prevent T-cell proliferation at the initial stages of naive T-cell activation.[6] Under physiological conditions, it hampers autoimmunity and limits immune activation, thereby minimizing the potential collateral damages to healthy cells and tissues. Inhibition of CTLA-4 is thus associated with a wide range of side effects resembling autoimmune reactions.[7] Several meta-analyses have shown that combination therapies can even increase the incidence and severity of irAEs, compared to monotherapies.[8–11] As a consequence, these detrimental side effects are the number one reason why patients abandon clinical trials using anti-CTLA-4 ipilimumab mono- or combotherapies.[8,9]

To solve this cruel problem, a current major effort in immuno-oncology consists in developing new antibodies with reduced toxic effects. One way to achieve such a goal is to improve the tumor-targeted immunoreactivity of these compounds, thereby lowering the systemic T-cell activation at the origin of irAEs. For this purpose, bispecific antibodies (BsAbs) represent perfect candidates, as their dual specificity directs them toward the tumor site, thereby minimizing the risk of irAEs. Among those novel BsAbs are MEDI5752 and ATOR-1015, recently developed by AstraZeneca and Alligator Bioscience, respectively.[12,13] The efficacy of these compounds was tested in immune checkpoint humanized preclinical models developed by genOway.

Uncoupling Toxicity from Therapeutic Efficacy: A Case Study on MEDI5752
Uncoupling Toxicity from Therapeutic Efficacy: A Case Study on ATOR-1015

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