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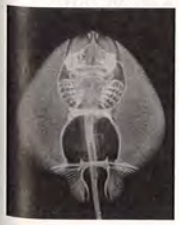

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Cancer immunotherapy comes of age

Ira Mellman[1], George Coukos[2] & Glenn Dranoff[3]

Activating the immune system for therapeutic benefit in cancer has long been a goal in immunology and oncology. After decades of disappointment, the tide has finally changed due to the success of recent proof-of-concept clinical trials. Most notable has been the ability of the anti-CTLA4 antibody, ipilimumab, to achieve a significant increase in survival for patients with metastatic melanoma, for which conventional therapies have failed. In the context of advances in the understanding of how tolerance, immunity and immunosuppression regulate antitumour immune responses together with the advent of targeted therapies, these successes suggest that active immunotherapy represents a path to obtain a durable and long-lasting response in cancer patients.

The passive transfer of anticancer monoclonal antibodies and donor T cells in the context of allogeneic bone marrow transplantation are effective treatments for a variety of haematological and solid malignancies[1]. Although not always thought of as 'immunotherapy', the success of these biotherapeutics probably reflects the ability of the donor cells or antibodies to induce an immediate immune reaction against the cancer, bypassing the requirement to activate endogenous immunity. These immune treatments have been well-established in oncology for several decades, and continued advances in antibody and T-cell engineering should further enhance their clinical impact in the years to come (Box 1).

In contrast to these passive immunotherapy strategies, the active stimulation of specific and durable antitumour immunity has proved elusive. In 1891, William Coley, a young New York surgeon, began intratumoral injections of live or inactivated *Streptococcus pyogenes* and *Serratia marcescens* in an effort to reproduce the spontaneous remissions of sarcomas observed in rare-cancer patients who had developed erysipelas[2]. Given Elie Metchnikoff's contemporaneous work demonstrating the immune system's ability to cause inflammation and destroy invading bacteria, 'Coley's toxins' made sense by acting to stimulate antibacterial phagocytes that might kill bystander tumour cells. Some significant responses were recorded over the ensuing 40 years, but successes were sporadic, difficult to reproduce and not obtained in a scientifically rigorous fashion. Superficial bladder cancer was one notable exception, for which the intravesical injection of live bacillus Calmette-Guérin after surgical resection was shown to prolong patient survival[3]. Other than this particular clinical setting, the approach was never embraced by oncologists who continued to rely on surgery and, increasingly, on effective new methods, such as radiation therapy and ultimately chemotherapy. Coley's strategy was further discounted due to the very real risks associated with the administration of infectious, or at least pyrogenic, agents to already weakened cancer patients; this is ironic given the trauma associated with the treatments that did come into common use. Thus began the history of cancer immunotherapy. Before continuing, however, it is useful to summarize what must happen to elicit a protective immune response to cancer, and why overcoming these barriers has been so difficult.

Generating anticancer immunity is a multistep challenge

Based on our current understanding of the immune response, there are three distinct steps that must be achieved, either spontaneously or therapeutically, to mount effective antitumour immunity (Fig. 1). To

BOX 1
Established immune treatments

Nine monoclonal antibodies targeting six cancer-associated proteins (Her2/neu, EGFR, VEGF, CD20, CD52 and CD33) are approved for the treatment of solid and haematological malignancies. In addition to antagonizing oncogenic pathways, these biotherapeutics may act by opsonizing tumour cells and triggering their death or removal by antibody-dependent cellular cytotoxity or phagocytosis[94]. Ongoing investigations in murine models and patients raise the possibility that they may also stimulate adaptive immune responses in some settings[95]. Recently, the successful conjugation of toxins to antibodies has been achieved, and these have induced a clinical response in patients who are refractory to the naked antibody[96]. The concurrent administration of immunostimulatory cytokines such as IL-2 and GM-CSF may also enhance the efficacy of antibody therapy.

Allogeneic bone marrow transplantation and the infusion of donor lymphocytes can be a highly effective therapy for some leukaemias and lymphomas[24]. The graft-versus-leukaemia effects involve the direct killing of tumour cells by donor lymphocytes, together with the subsequent induction of broader innate and adaptive reactions. On the basis of these clinical benefits, many groups are exploring the use of adoptive T-cell therapy in the autologous setting. Promising strategies include the use of lymphodepletion before T-cell infusion, and the engineering of new T-cell specificities with CARs[97].

Other immune treatments that have received the FDA approval include recombinant cytokines, such as IL-2 (Proleukin), which is used for melanoma and renal cell cancer. Response rates are low (~15%) and the significant risk of serious systemic inflammation requires administration as an in-patient. Interferon-α is another agent that gained approval for 'immunological cancers' (that is, melanoma or renal cell cancer). Although also associated with low response rates and high-dose toxicity, a small subset of melanoma patients, who are also predisposed to autoimmunity, has been shown to exhibit an impressive survival response[98]. It has been, however, difficult to pre-identify these patients, which limits the use of the approach. Yet, when seen, responses are durable, suggesting they reflect active antitumour immunity.

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