CANCER IMMUNOTHERAPY COMES OF AGE (FINALLY!)

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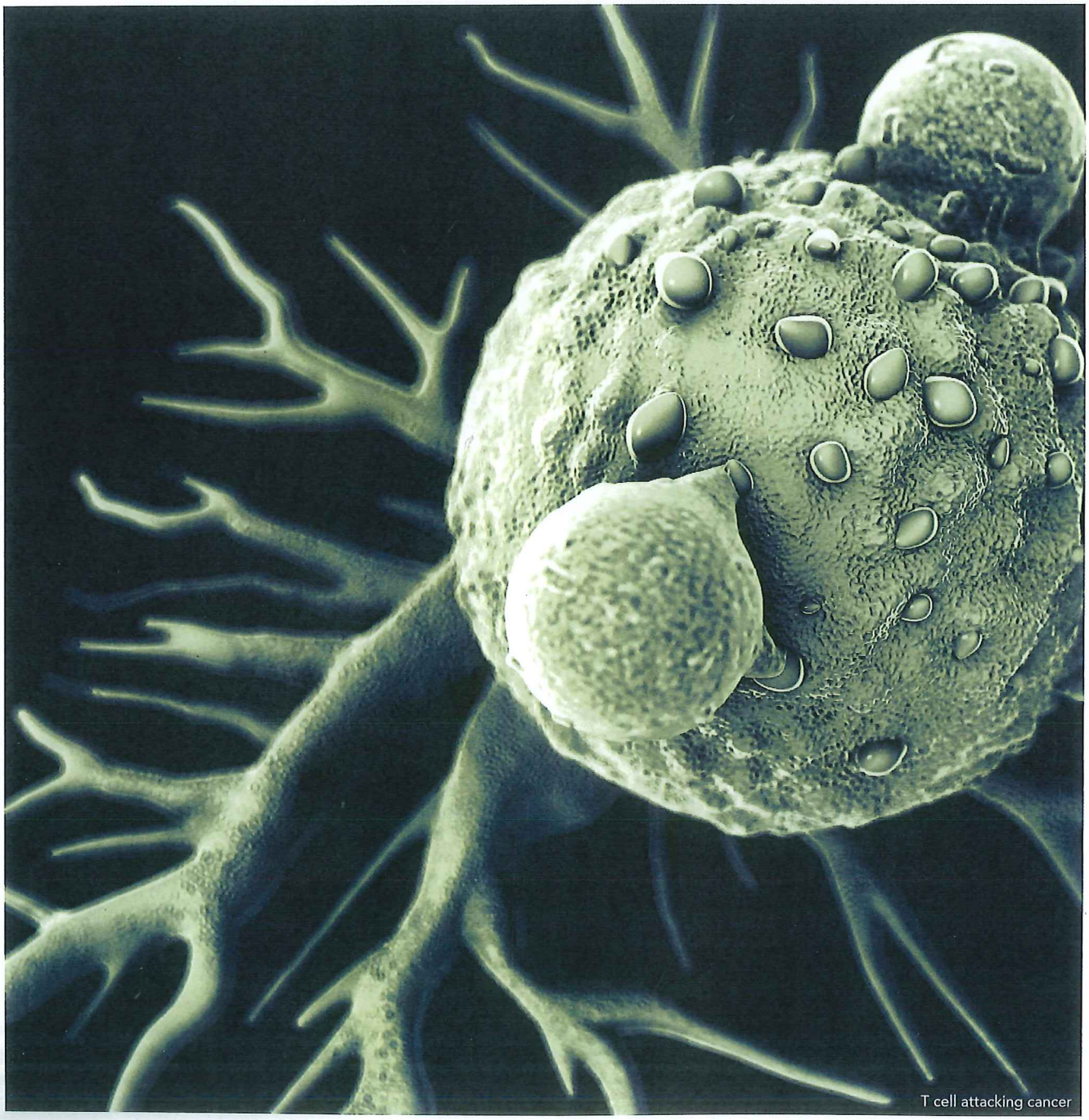

T cell attacking cancer

'Immuno-oncology' is the current buzzword in cancer treatment, with drugs like pembrolizumab (KEYTRUDA®) and nivolumab (Opdivo®) providing exciting new treatment options for an expanding range of tumour types, including melanoma and lung cancer. The ability to activate the immune system to kill cancer cells has become a focus area for oncology drug discovery and development.

Manipulation of the immune system to control cancer is not a new concept; however, the idea can be traced back to at least the 1890s, when William Coley began treating patients with a preparation from streptococcal cultures (Coley's toxins) to stimulate immune activity. The use of the BCG (Bacillus Calmette-Guérin) vaccine for the treatment of bladder cancer was an ultimate outcome from Coley's original concept. Despite these early hints of efficacy, enthusiasm for immune system involvement in (and control of) cancer has waxed and waned over the subsequent years.

In the 1960s and the following decades, tumour immunology again came to the fore as a result of studies into the rejection of tumour transplants. It became clear that the immune system had an ability to distinguish 'normal self' from 'tumour self', and a number of tumour-associated antigens (TAAs) were identified. This opened up the prospect of immunising against cancer and, during the following years, development of the first generation of cancer vaccines, which, at best, yielded anecdotal evidence for patient benefit.

The modern era of cancer immunotherapy began with the advent of recombinant DNA technology and the emergence of the biopharmaceutical industry. Early initiatives included the development of immune-stimulating cytokines, such as the interferons (for example IFN-a, IFN-g) and interleukins (for example IL-2). Although these drugs were approved for use in niche cancer (and other) indications, their severe side effect profiles and limited efficacy meant that the early expectations for these drugs as the 'silver bullets' for the treatment of cancer were never realised.

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Over the same period, advances in DNA sequencing provided new insights into cancer cell biology, and provided the impetus for a new generation of therapeutic cancer vaccines. Throughout the 1990s and into the 2000s, multiple variations on the cancer vaccine theme (whole cells plus or minus immune-stimulating cytokines, cell lysates, subunit vaccines, DNA vaccines, et cetera) have been taken into the clinic. These products have generally shown excellent safety profiles, and occasionally evidence for the induction of relevant immune responses, but they have rarely shown any meaningful efficacy. The sole exception was Dendreon's sipuleucel-T (Provenge®) for the treatment of advanced prostate cancer, which was successful in gaining market approval in the United States and European Union, but was a commercial disaster. The failure of multiple cancer vaccines over the past 20 years has dampened enthusiasm for cancer therapeutic vaccines (at least for the time being).

Dr Ian Nisbet

In contrast to the experience with cancer vaccines, the use of antibodies as effector molecules, receptor antagonists or drug-targeting agents has blossomed since the 1990s. Drugs such as rituximab (Rituxan®), trastuzumab (Herceptin®), cetuximab (Erbitux®) and many others have become established as standards of care across a range of tumour types. While not necessarily acting strictly as immunotherapies, these products have a demonstrated the power of leveraging one arm of the immune system (the humoral arm) for the treatment of cancer.

More recently, a greater understanding of the ways that tumour cells evade and block the immune system has opened up new treatment paradigms. Thanks to the pioneering work of James Allison, chairman of Immunology at The University of Texas MD Anderson Cancer Center in Houston, Texas, and others, we now appreciate the complexity of the relationship between cancer cells and the immune system. We now know that cancer cells can deactivate killer T cells through checkpoint pathways; that they can block T cell infiltration by the expression of galectins and other inhibitory molecules; and that they can downregulate the expression of MHC class 1 molecules, and thereby make themselves largely invisible to the immune system. Clearly, cancer cells can manipulate the immune system not to kill them, and understanding the protection mechanisms has provided opportunities for drug developers to out-manipulate the manipulators.

KEYTRUDA®, Opdivo® and YERVOY® are known as checkpoint inhibitors (they block checkpoint pathways). KEYTRUDA® and Opdivo® block PD1-PDL1 signalling between tumours and immune cells, while YERVOY® blocks a separate tumour cell/T cell engagement pathway (namely CTLA4-CD28). In doing so, these antibodies release a cancer-induced 'handbrake' on the immune system, resulting in dramatic anti-tumour responses. In melanoma, previously unheard-of response rates of around 30 per cent have been achieved in late-stage patients. As impressive and unprecedented as these response rates are, there is clearly substantial room for improvement—a 30 per cent response rate still means that the majority of patients are not deriving benefit from the treatment.

> So, where to from here? It is reasonable to argue that we are still in the early stages of the immuno-oncology revolution

One way that is being actively explored to increase response rates is for immunotherapies to be used in combination with themselves, or with other therapies. Again in melanoma, the combination of Opdivo® with YERVOY® has pushed response rates into the 50 per cent and above range; however, the extra activity comes at a cost—both financially and clinically. High-priced therapies (often at a cost of more than $100,000 per patient per annum per drug) create challenges for the healthcare system. For the individual, doubly activating the immune system increases the incidence and severity of side effects: particularly debilitating inflammatory conditions, such as inflammatory bowel disease. The immune system is a powerful beast, and there are good reasons why it is subject to natural control mechanisms such as checkpoints.

On the treatment horizon is a range of cellular therapies, which represent another dimension of the immuno-oncology arsenal. It is now possible to engineer and expand T cells targeting specific TAAs by transfecting the cells with chimeric antigen receptors (CARs) to create CAR-T cells. These cells do not need to be activated through the normal T cell activation pathways; they are ready to seek out and destroy tumour cells expressing the cognate TAA. In clinical trials in patients with rare leukaemias, such as acute lymphoblastic leukaemia (ALL), response rates of 95 per cent have been achieved using CD19-targeted CAR-T cells in patients who have failed all existing therapies. To describe this as unprecedented is a gross understatement! However, despite such extraordinary results (and the associated optimism and hype), the CAR-T approach is yet to prove itself in other tumour types, particularly solid tumours.

Finally, another form of cellular immunotherapy that is beginning to gain momentum is to leverage the innate immune system, particularly through the activity of natural killer (NK) cells. Mechanisms for the activation of endogenous NK cells are being explored, as is the infusion of exogenous NK cells. In some ways, this brings the field of immuno-oncology full circle. It is now known that bacterial cell components are natural activators of the immune system (through, for example, binding of bacterial DNA to toll-like receptors on immune cells), and it is quite likely that the occasional beneficial effects obtained with 'Coley's toxins' were due, at least in part, to non-specific stimulation of innate immunity.

So, where to from here? It is reasonable to argue that we are still in the early stages of the immuno-oncology revolution. It is also reasonable to argue that prior oncology drug development efforts (whether successful or not) needs to be reconsidered in light of treatments such as checkpoint inhibitors. It is likely that treatments like cancer vaccines, and even chemotherapy, may be much more effective in the context of an immune system 'with the handbrake released'. Similarly, other emerging approaches, such as oncolytic viruses, need to be assessed in combination with checkpoint inhibitors. There is a huge amount of work to be done, both pre-clinically and clinically.

One thing seems certain: after a gestation period of more than a century, manipulating and using the immune system to treat existing disease, as well as to prevent disease recurrence, will finally be entrenched as a central feature of cancer therapy.

Dr Ian Nisbet is a partner in the biotechnology consulting company Afandin Pty Ltd. He is actively involved in cancer drug development, with multiple companies; he is the part-time CEO of Cancure Pty Ltd, which is developing a portfolio of cancer drugs that includes both immunotherapies and targeted therapies; he is a co-founder and executive director of Senz Oncology Pty Ltd, which is developing a small-molecule treatment for acute myeloid leukaemia (AML); he is a co-founder and corporate adviser to Cartherics Pty Ltd, which is developing a next-generation CAR-T platform; and he is chairman of vivoPharm Pty Ltd, a preclinical contract research organisation that specialises in cancer pharmacology. He is also an Industrial Fellow at the Australian Institute for Bioengineering and Nanotechnology (AIBN) at the University of Queensland.