

Commentary: Richard Goodfellow

Why checkpoint inhibitors need help

Cancer immunotherapy is emerging as the biggest drug development story of the decade. At last, patients with previously untreatable conditions are being given a new lease of life – and the developments are continuing at a frenetic pace as the pharmaceutical giants jostle for position. The breakthrough has been spearheaded by the discovery of the ‘checkpoint inhibitors’ which liberate the immune system by blocking the pathways that allow cancer cells to hide tumours from immune attack.

In this way, checkpoint inhibitors can enable the host immune system to resume its ability to recognise, attack and destroy cancer cells. The first checkpoint inhibitor, the antibody ipilimumab (Yervoy; Bristol-Myers Squibb Inc) is already on the market and other drugs blocking PD-1 and its ligand PD-L1 are in advanced clinical trials with the first likely to be approved as soon as 2015. However, checkpoint inhibitors cannot work on their own if the patient fails to mount an adequate immune response to the tumour or if the tumour evolves so that it is no longer recognised by the pre-existing immune response. This may apply to well over 50% of melanoma patients, especially those with late-stage disease, and to an even higher percentage of patients with less immunogenic solid tumours that have not been caused by chemical carcinogens or ultra violet light.

And so a new race has begun – before the checkpoint peloton has even completed the first lap. The PD-1 drugs seem to be the common denominator. They are being combined with anti-CTLA-4 drugs such as ipilimumab (Yervoy); with tyrosine kinase inhibitors such as sunitinib (Sutent; Pfizer Inc) and erlotinib (Tarceva; Roche); with the anti-CD27 antibody varlilumab (Celldex Therapeutics Inc); with the BRAF inhibitor vemurafenib (Zelboraf; Roche) and many others. However it has already been found that combining two relatively non-specific drugs can produce serious side effects.

Can cancer vaccines be the next leap forward?

Taking the brake off T cells with checkpoint inhibitors whilst simultaneously pressing the accelerator using active immunotherapies is a logical next step towards overwhelming disease and increasing efficacy, without the burden of more serious and even fatal side effects. Cancer vaccines can stimulate *de novo* immune responses but, until recently, none of the vaccines in clinical development have been able to induce potent T cells with the power and specificity to recognise and kill tumour cells. In general, peptides stimulate low avidity responses that fail to recognise tumour cells and there was no evidence of synergy when a melanoma-derived peptide vaccine was combined with ipilimumab. A whole antigen MAGE protein vaccine also failed to show a significant survival advantage in both melanoma and lung cancer, even in the presence of a strong adjuvant. A Phase 3 study of a virus encoding GM-CSF (T-Vec; Amgen Inc) has recently shown some promising results. However, potential patients must have tumours

that are accessible for direct injection and the vaccine is less effective against distant, inaccessible tumours. Despite these disadvantages, Amgen (T-Vec) and Merck (MK-3475) are moving ahead to evaluate a combination strategy. Adoptive transfer of *ex vivo* expanded T cells has also shown encouraging results. However, these approaches are patient-specific, time-consuming and expensive. There is therefore still a need for a simple, safe and effective vaccine able to induce potent and specific killer T cells.

We would argue that this advantage can be obtained by using the power of dendritic cells, the ‘generals of the immune response army’, to stimulate a whole host of immune ‘foot soldiers’ including high avidity, highly potent T cells to attack pre-determined targets on cancer cells. Our approach is illustrated by our first product, SCIB1, which is a DNA plasmid encoding an antibody with four melanoma-specific T cell epitopes grafted into its structure. Recent advances in delivery technologies have enabled DNA vaccines to come to the forefront of vaccine research. One of the most successful has been the use of electroporation, which uses electrical fields to increase DNA drug delivery efficiency by up to 1000-fold compared with conventional injection. The approach has recently been validated commercially through deals between Ichor Medical Systems Inc and Pfizer Inc and between Inovio Inc and Roche. We use electroporation in conjunction with intramuscular injection to deliver SCIB1 to patients. This results in the direct uptake of DNA into cells and also enhances the immune response by targeting the expressed hybrid antibody to dendritic cells via the CD64 receptor.

The latest data from a Phase 1/2 clinical trial of SCIB1 in patients with advanced melanoma has shown high immune response rates, evidence of prolonged survival and tumour destruction plus a very benign side effect profile. Median survival time in patients with Stage III/IV disease is now 30 months since patients entered the study. Patients with resected Stage 4 disease are all still alive 19-41 months since their tumours were removed. This compares extremely favourably with published survival rates for patients with resected disease where 50% of Stage IV patients usually die within 21 months of surgery. We believe the induction of *de novo* immune responses and evidence of disease control provide a persuasive logic to combine SCIB1 with a checkpoint inhibitor to treat cancer.

For the first time we are glimpsing a future in which cancer could be viewed as a chronic disease like diabetes or hypertension. The ability to deliver T cells that are unleashed by checkpoint inhibitors in a hostile tumour environment or, even more exciting, to be able to stimulate and maintain a potent T cell response in patients with immunotherapies such as ours offer a compelling prospect.

This commentary was written by Richard Goodfellow, joint chief executive officer, of Scancell Holdings Plc in Nottingham, UK.