Commentary: Eliot Forster

Hot targets in immuno-oncology

The successful roll-out of Covid-19 vaccines in Europe and North America has brought into sharp focus the power of the human immune system. Combined with the strength and ingenuity of the biomedical sector, these vaccines have been the primary source of hope that the world can return to some kind of normality. Never before has the general population been so interested or invested in how antibodies and antigens function, or the role of T cells in fighting disease.

In this article, I explain why there is reason to be optimistic about cancer treatment as well. At F-star Therapeutics Inc, the company that I lead, we are working on treatments that can help patients who don't respond to current drugs, to control or even overcome their disease.

In oncology, just as with the new Covid-19 vaccines, the possibilities presented by harnessing or modifying the body's own immune system is a focus of huge interest. The term immuno-oncology (IO) may be recent, but the concept of modulating a patient's immune system to treat cancer goes back at least to the 19th century with attempts by William Bradley Coley to treat bone cancer with immune modulation. In more recent times, immunotherapy took a leap forward with the discoveries of James Allison and Tasuku Honjo of proteins that can act as brakes on the immune system. By blocking the activities of these proteins, called PD-1 and CTLA-4, scientists were able to show that the antibodies, or immune checkpoint therapy, could unleash T cells to fundamentally change the outcome of some patients with advanced cancer.

Since the first regulatory approval of the checkpoint inhibitor pembrolizumab for advanced melanoma in 2014, many immuno-oncology targets have been tested in the clinic. Over the past three years, the immuno-oncology pipeline has grown by 230% and there are now in the region of 4,720 agents acting on 500 targets. PD-L1 (programmed death-ligand 1) has been the most successful and promising of these targets.

However not all patients with advanced cancer respond to these therapies – as many as 80% do not. There continues to be a large unmet medical need where patients do not see a durable response from currently approved medicines. In the quest for the next generation of immunotherapies, biotech and pharma companies continue to search for the next blockbuster therapy. Approaches range from stimulating or agonising immune cells to blocking or antagonising other receptors. A wide range of new targets have been explored but many were only marginally effective and in most settings, disappointing at best.

There is new hope however. Recently targets such as LAG-3 (lymphocyte activation gene 3) and CD137 (4-1BB), a member of the tumour necrosis factor receptor family, have been gaining prominence in the clinical setting. Data presented at a meeting of the Society for Immunotherapy of Cancer in November 2020 were particularly promising for CD137. Presentations at the conference highlighted the role of CD137, a positive regulator of the immune system in cancer treatment. CD137 is upregulated on activated T cells of the adaptive immune system and on NK cells of the innate immune system. A very recent readout in a study in skin cancer patients by Bristol Myers Squibb Co for the anti-LAG-3 antibody, relatlimab, was highly encouraging. The large phase 3 trial met its primary endpoint of progression-free survival.

At F-star we are particularly focused on LAG-3 and CD137 as well as PD-L1 as targets for our bispecific antibody products. The founders of F-star discovered that a few simple amino acid substitutions in the Fc region could produce novel, high affinity, bivalent binders for the next generation of cancer treatments. Our proprietary mAb2 bispecific platform has a natural antibody structure for ease of manufacture, and low immunogenicity risk. The tetravalent binding (with '2 plus 2' binding sites) has a 'sweet spot' in targeting receptors such as LAG-3, CD137 and PD-L1 to give enhanced potency and stronger bispecific clustering to trigger immune cell activation in the tumour.

Our most advanced program is FS118, which rescues PD-1 inhibitor failures, and currently is in a Phase 2 clinical trial in head and neck cancer patients, targeting PD-L1 and LAG-3. In a broad cancer patient population, all of whom were PD-1 inhibitor failures, FS118 showed a 59% disease control rate in a Phase 1 trial and was well-tolerated up to 26 months of dosing. For us, success will be transforming the lives of patients, and being able to give a patient two Christmases he or she might not have been expecting to have.

Our second drug, FS222, is designed to improve outcomes in PD-L1 low tumours and is currently in a Phase 1 trial in the recently de-risked, but competitive, PD-L1/CD137 space. A third drug, FS120, is designed to create safe and targeted triple activation of the immune system in the tumour to improve checkpoint inhibitor and chemotherapy outcomes, by stimulating both CD137 and OX40, another co-stimulatory molecule. It is currently in a Phase 1 monotherapy clinical trial and we expect to quickly move into a combination trial with a commercially approved PD-1 inhibitor.

Over the next few months we'll be sharing new data from these three trials which we hope will further reinforce the potential of LAG-3 and CD137 in immuno-oncology. The possibilities to transform the lives of patients will be the reason for persisting and refining our tetravalent bispecifics.

Dr Özlem Türeci, a cancer immunologist and one half of the team behind the Pfizer-BioNTech Covid-19 vaccine, has spoken of the motivation to provide solutions to patients. Science, in her view, is the 'tool' to achieve it: "I think the most noble thing you can use science and technology for is to serve the people," she said in a recent newspaper interview.

Dr Eliot Forster is the chief executive of F-star Therapeutics Inc.

©2021 Evernow Publishing Ltd