Commentary: Erik Manting

The hunt for the perfect tumour-associated antigen

The field of cancer immunotherapy has diverged over recent years into two opposing schools of thought: one based on common, shared tumour antigens and the other on highly specific, even individualised neoantigens. Disrupting tumour immune tolerance - turning immunologically 'cold' tumours 'hot' again - is the common goal but the two strategies differ in their approaches for achieving it.

At the heart of this divergence is the question of which cancer antigens to target, and how to find them. For immune-based therapies to specifically attack cancer cells and not the rest of the body, the target antigens need to be present selectively on cancer cells and not, or at much lower levels, on healthy tissues. Ideally, they should also be highly immunogenic and capable of triggering a strong immune response. If the therapy is to benefit more than a select few, the antigens must be expressed across many patients with a particular tumour type. Despite decades of research and hundreds of millions of dollars spent searching for cancer antigens with these optimal qualities, ticking all three boxes has proved to be no easy task.

Continual advances in our understanding of cancer cell biology have resulted in the identification of dozens of tumour-associated antigens (TAA) that could serve as the basis for cancer vaccines or other cancer immunotherapies, including well-known proteins like WT1, p53 and MUC1. For many of these antigens, specific changes in structure or expression level are hallmarks of cancer cells' accelerated and uncontrolled replication, their characteristic metabolic adjustments, or their higher mutation rate, distinguishing them from the protein repertoire found on healthy cells.

Despite the many years of research and detailed characterisation of many different TAAs, it has been extremely difficult so far to formulate effective cancer vaccines or other cancer immunotherapies based on individual TAAs, leaving this class of therapies without consistent clinical success. This may relate to the fact that the immune system is trained via negative selection to not recognise proteins expressed by the body's own cells, in order to avoid damaging auto-immunity. TAAs are typically so close to normal, or 'self' antigens that they fail to trigger strong immune responses. Instead, immune surveillance of cancer cells may depend on different immune cells acting in concert and multiple TAAs contributing to the total immune response.

If effective cancer immunity indeed acts like a 'carpet bomb', requiring combined immune responses against multiple tumour associated antigens, then the best place to start for a cancer vaccine could be the attenuated version of an actual cancer cell. In other diseases, such as bacterial and viral infections, an attenuated version of the disease-causing agent has often proved the most effective basis for a vaccine. However, cancer cells are poorly immunogenic and possess multiple mechanisms to avoid recognition by the immune system.

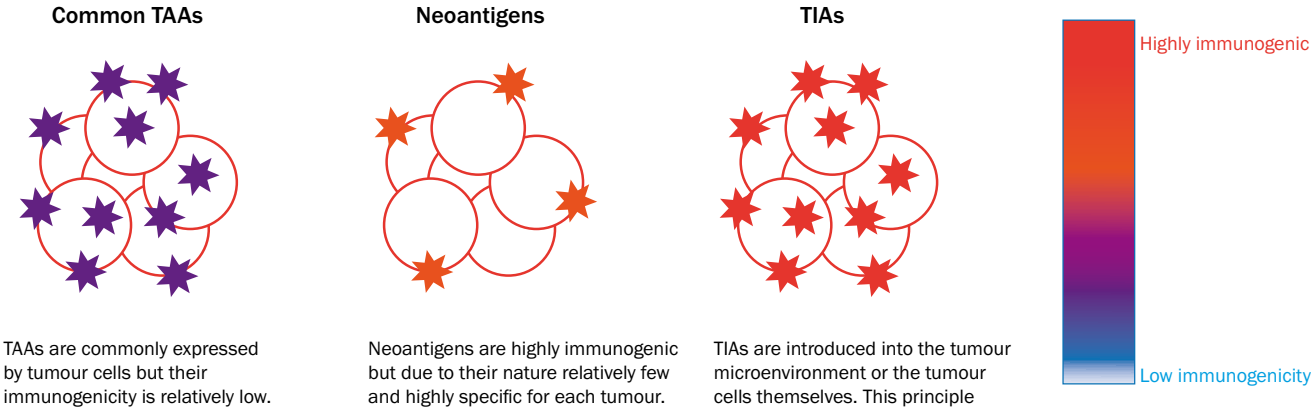
To overcome this hurdle, our company DCprime has developed a platform comprising the DCOne leukaemic cancer cell line and a proprietary manufacturing process in which the phenotype of DCOne cells is shifted towards that of a mature dendritic cell (DC). Dendritic cells (DCs) are decorated with stimulatory molecules that activate immune cells and their typical role in the immune system is to initiate or 'prime' different parts of the immune system upon encountering infectious agents or tumour cells. By shifting DCOne leukaemic cells towards a DC phenotype, the cells become highly immunogenic and trigger multifunctional immune responses against multiple TAAs. This forms the basis for our lead product DCP-001, a cancer relapse vaccine which is currently being tested in an international Phase 2 clinical study to delay or prevent tumour recurrence in acute myeloid leukaemia (AML) patients suffering from residual disease. The Phase 2 study is based on results from our earlier Phase 1 study, in which promising overall survival was observed, next to multifunctional immune responses against multiple TAAs. Interestingly, the responses were not limited to those TAAs which are expressed by the DCOne cells, but also comprise responses against other TAAs, indicating a broadening of the immune response against the tumour. This phenomenon called 'antigen spreading' or 'epitope spreading,' has been associated with clinical responses and the maintenance of efficient anti-tumour immune responses in different cancer immunotherapies.

The main observed side effect associated with the product has been temporary redness of the skin at the site of injection. This benign safety profile makes it a highly suitable solution for those patients who have just undergone aggressive cancer treatment such as chemotherapy and who require additional treatment to prevent disease recurrence or relapse. We are currently testing this relapse vaccination approach in a Phase 2 clinical study in AML and expect to start additional studies in ovarian cancer and myelodysplastic syndrome. The 'gentle' nature of the product merits its testing in additional indications where the immune system could contribute to control residual disease, possibly in combination with other available therapies.

Catalysed by advances in DNA sequencing, 'omics' technologies, and artificial intelligence, the search for novel, stronger antigens has accelerated in recent years. These technologies have enabled the identification of highly specific 'needle in the haystack' tumour antigens that may vary from individual to individual.

If whole cell-based vaccines like DCP-001 can be described as immunological 'carpet bombs,' neoantigen-based therapies are more akin to homing-missiles. Neoantigens stand out from other protein sequences in that they are highly tumour-specific, immunogenic, and are presented by cancer cells to the immune system. But because there is strong negative selection pressure on cancer cells expressing such neoantigens, they are much rarer and harder to find. They are also far less likely to be shared across patients compared with common TAAs, meaning that immunotherapies

Figure 1



TAAs are commonly expressed by tumour cells but their immunogenicity is relatively low. Vaccination approaches rely on raising the level of immunity against single or multiple TAAs. DCP-001 is a whole cell-based vaccine carrying multiple endogenous TAAs.

Neoantigens are highly immunogenic but due to their nature relatively few and highly specific for each tumour. Therefore they require a relatively complex, individualised approach.

TIAs are introduced into the tumour microenvironment or the tumour cells themselves. This principle overcomes current limitations of TAAs (low immunogenicity) and neoantigens (rare, highly specific antigens) and could provide a new, off-the-shelf basis for cancer immunotherapies.

targeting neoantigens must be highly personalised, trading broad accessibility for higher specificity.

Next to their complex identification and formulation, the main challenge for neoantigen-based immunotherapies is the prospect of tumour immune escape. Tumours may evolve to reduce antigen presentation on their cell surface, lower expression of the neoantigen, or even get rid of it completely to avoid detection by the immune system.

The success of neoantigen vaccines may therefore also rely on efficient epitope spreading, which is why we often see cancer vaccines designed to target multiple neoantigens at once in order to be effective before immune response diversification by epitope spreading occurs. It has also been suggested that a combination of vaccination strategies based on TAAs and neoantigens may result in more profound triggering of epitope spreading.

Tumour-independent antigens: a new horizon?

There may however be an entirely new way of approaching the problem. What if, instead of adapting the therapy to fit the cancer's antigen profile, we could adapt the cancer's antigen profile to fit the therapy? This is the premise of the tumour-independent antigen (TIA) concept, whereby the cancer is 'tagged' with a highly immunogenic foreign antigen of choice, perhaps even one that the patient's immune system already recognises, such as a virus-specific antigen or an antigen encountered through past vaccination. Instead of developing a therapeutic 'key' to fit an imperfect antigenic 'lock' - often a lengthy and difficult process - we would instead select a lock and key combination that we already know works well *in vivo*, and use it to direct the immune response towards the tumour.

The implications of such an approach would be profound. Cancer immunotherapies would no longer be limited to the antigens that just happen to be present on a tumour, constrained by the cancer's chaotic mutational landscape. Rather, we could leverage the growing repository of known, safe, highly immunogenic antigens and plant them directly onto the tumour or around its microenvironment, marking it as an easily recognisable target for the immune system once an immune response has been induced against the antigen.

The results of a preclinical proof-of-concept study, which DCprime presented last year, have already shown that this TIA vaccination concept is indeed effective in eliciting and directing a robust immune response to the tumour site in mouse models. In that study, we injected irradiated DCOne cells with a dendritic phenotype (mDC) carrying a foreign antigen into the tumour, and flagged it, after we had induced immunity against the antigen via vaccination. We found that tumour growth was slowed in both glioblastoma and melanoma mouse models compared with controls. This was backed up by the presence of significantly more antibodies against the exogenous antigen in the serum of these mice than in the controls. DCOne cells can thus be used as an intratumoural carrier of exogenous antigens.

Based on these promising initial results, DCprime is building out the TIA-based immunotherapy concept and is developing different methods to allow for tumour labelling, next to intratumoural administration using the DCOne platform. We have also recently announced a collaboration with PCI Biotech of Norway to test the potential use of photochemical internalisation technology for this purpose. We believe that making cancer immunotherapies independent of the current limitations of tumour-associated antigens and relying on other, more optimal antigens of choice has the potential to revolutionise the field.

This article was written by Dr Erik Manting, chief executive officer of DCprime of the Netherlands.