How Immune Priming Could Make More Patients Eligible for Immunotherapy

Researchers are investigating whether antibody drug conjugates (ADCs) have the potential to reengage the immune system to make more patients, including those previously resistant to treatments, eligible for checkpoint inhibitor therapy

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Checkpoint inhibitors have changed the game in cancer treatment over the last decade, but many patients are still unable to benefit from these immunotherapies, due to mechanisms tumours evolve, which overcome the body's immune response. Because of this, researchers are increasingly interested in adjunct therapies that can 'prime' the immune system by boosting the efficacy of T cells. This strategy could potentially allow checkpoint inhibitors to work in a broader spectrum of patients, including those previously ineligible for such treatments.

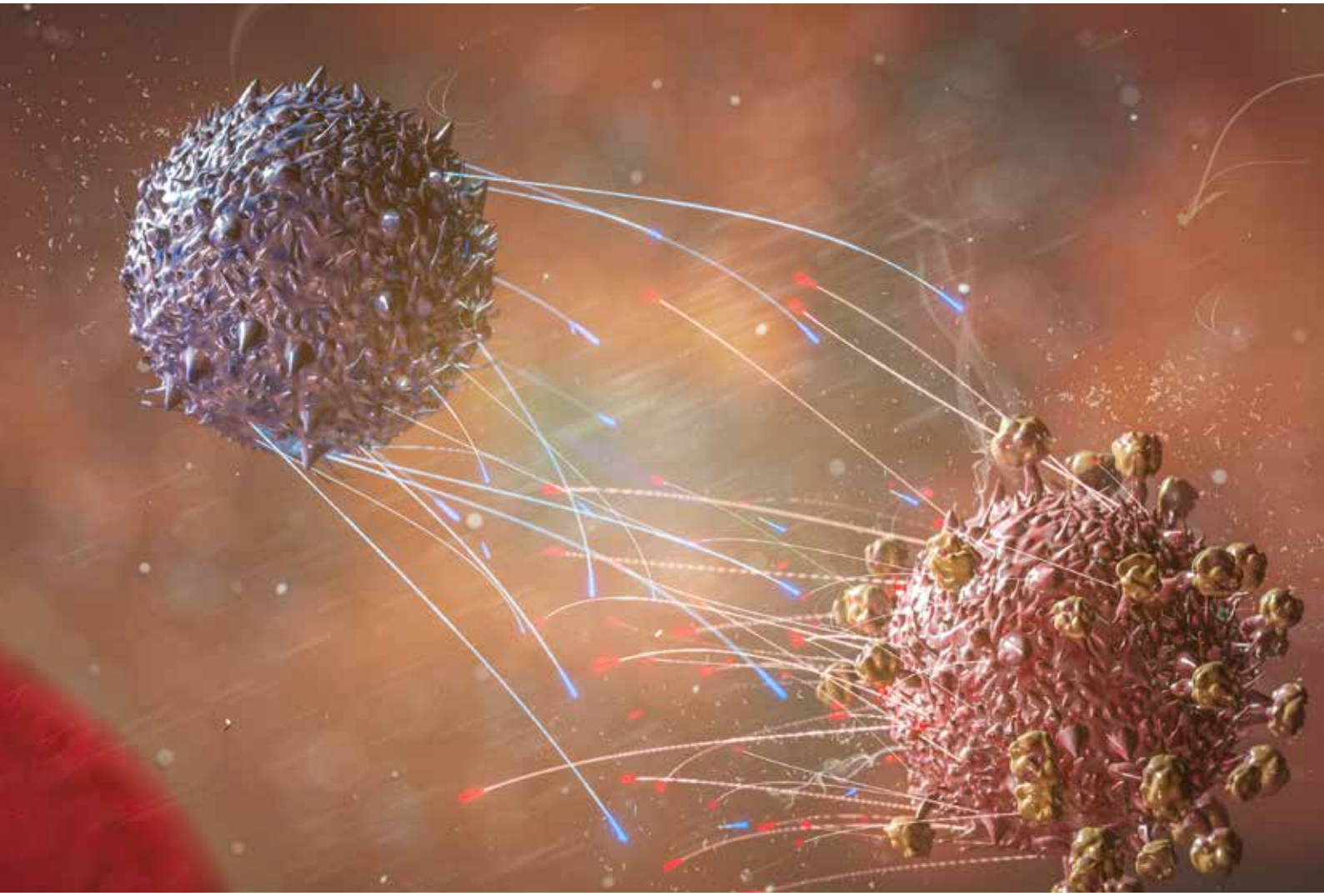
Tumours can only progress by evading the immune system, and, as such, many tumours evolve to exploit immune checkpoints – inhibitory proteins, which regulate immune activation. In healthy individuals, these checkpoint proteins turn the immune response 'off', to maintain self-tolerance and prevent the destruction of healthy cells. This is achieved by checkpoint proteins binding to receptors on the surface of T cells, to prevent them from acting.

By having these proteins on the surface of cancer cells, tumours are able to turn off T cells, and evade the immune system. Checkpoint inhibitor treatment counters these mechanisms by blocking the checkpoint proteins present on the surface of cancer cells – such as PD-L1 or TLA-4. This prevents the 'off' signal from being sent to T cells, which subsequently remain active, and able to target cancer cells. However, in many cases, tumours – especially solid tumours – become resistant to checkpoint inhibitor therapy when they acquire mutations independent of the checkpoint protein mechanism of evasion. Research published in JAMA Network Open suggests that only a third of cancer patients in the US are eligible for checkpoint inhibitor therapy – leaving much room for growth within this space.

Indeed, some of the initial excitement surrounding checkpoint inhibitor therapy has been dampened by late-stage trial failures in some cancers, suggesting that these therapies are suitable for fewer patients than initially hoped. The research also estimates that up to 9% of people who were eligible for immune checkpoint inhibitors in 2018 subsequently became ineligible because of negative confirmatory trials.

In urothelial cancer, this has led the FDA to revise the labels of Keytruda (pembrolizumab), and Tecentriq (atezolizumab), to limit the number of people these drugs are recommended for. Furthermore, in order to be eligible for PD-1 inhibitor therapy for lung cancer, for example, patients may need to have their cancer cells tested in order to confirm they have high enough levels of the PD-L1 protein on the tumour.

In recent years, this has resulted in an increased interest in drugs that can sensitise otherwise ineligible patients in such a way as to make them eligible for checkpoint therapy, boosting the body's immune response against cancer.



ADCs and Reactivating the Immune System

Of course, checkpoint inhibitors aren't the only form of immunotherapy available to patients. ADCs represent a significant area of interest for the treatment of cancer, with 12 ADCs on the market and over 90 in clinical development. ADCs have been designed to link an antibody with a biologically active cytotoxic payload, enabling the targeted delivery of a drug to tumours directly, thus avoiding toxicity to healthy tissues.

> *There remains an unmet need for effective therapies in many patient populations*

Recent research has also shown that ADCs have the potential to reengage the immune system. However, there remains an unmet need for effective therapies in many patient populations (1). Of the 12 ADCs approved for clinical use, seven are approved for use in specific haematological malignancies while three target specific subtypes of breast cancer. The other two target urothelial and cervical cancer.

One current mechanism of interest involves a type I transmembrane glycoprotein called CD205 with immunosuppressive properties. The CD205 receptor is highly overexpressed in solid and liquid tumours, including in gastric, lung, and ovarian cancer, and supresses the body's immune system from destroying the tumour. It plays an important role in removal of apoptotic and necrotic cells by the immune system, and in determining the cellular phenotype and invasiveness of some types of cancer (2, 3).

CD205 has unique characteristics that make it an ideal target for ADC therapy – namely, its differential cell surface expression in multiple human cancers compared with healthy tissues, and its presence on immune inhibitory cells.

The hope is that a dual action ADC, targeting the CD205 protein on a) cancer immune inhibitory cells to reverse immune suppression, and b) the cancer cells directly, will show strong antitumor activity.

In this case, targeting CD205-expressing cells may not only remove cancer cells, but also allow the immune system to reset and restart in an immunogenic direction by selectively depleting regulatory cells, and preventing T cell activation and proliferation.

Immune 'Priming'

Researchers now have reason to believe that such ADCs can reengage the immune system in a way that is also beneficial to checkpoint inhibitor therapy. While analysing translational data from a recent clinical study evaluating a CD205-targeting ADC, researchers unexpectedly found that increases in PD1+ T cells and T cell induction occurred simultaneously with decreases in immuno-suppressive CD4+ CD205+ and CD8+ CD205+ cells, coinciding with rapid resolution of the primary tumour, lymph node metastases, and ascites in patients with advanced tumours (4).

These findings suggest that targeting CD205 in this way activates the patient's immune response against the tumour through a potentially novel mechanism: drug-induced depletion of CD8+ CD205+ immuno-suppressive cells, which subsequently activates T cells.

The study findings also suggest that combining these drugs with checkpoint inhibitors could achieve favourable clinical outcomes by 'priming' the immune system. Indeed, near complete responses were seen in two chemo-refractory advanced cancer patients with low PD-L1 expression after 2-5 cycles of a CD205-targeting ADC followed by 1-2 cycles of a checkpoint inhibitor. Prior to treatment with the CD205-targeting ADC, such patients were ineligible for anti-PD-1 treatments due to their low PD-L1 status.

The data was presented at the 2022 American Association of Cancer Research (AACR) Annual Meeting, and further research is planned to follow up on this potentially promising mechanism of action.

Research in other areas has suggested similar effects can be induced via other targets, such as the combination of a monoclonal agonist of signal-regulatory protein alpha (SIRP-α) with an anti-PD-1, where promising results have been seen in heavily pre-treated solid tumour patients. Another drug candidate is a PEGylated IL-2 (the addition of polyethylene glycol to IL-2), which is designed to activate and induce proliferation of CD8 T-cells and NK cells. Breakthrough therapy designation was granted for combination of this IL-2 drug with an anti-PD-1 for treatment of advanced melanoma – however, it has so far shown no benefit for patients in the clinic compared to the control arm.

Looking to the Future

There is still much we don't understand about the human immune system and how it interacts with cancer – but our knowledge is growing every day. Several biotech companies are focused on solving the problem of how to improve outcomes for patients with solid tumours who respond poorly to PD-1 inhibitors and other checkpoint inhibitor therapies – and Big Pharma is starting to take interest via partnerships and their own research.

Ultimately, cancer is too diverse a disease to ever allow for one single treatment approach to dominate. However, by developing therapies against a multitude of different targets, and in a variety of combinations, we can help give patients with high unmet need the best possible chance of finding an effective treatment that works for them.

References

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Dr Christian Rohlff is CEO and founder of **Oxford BioTherapeutics**, a clinical stage biotech company focused on first-in-class immune therapies, including ADCs, with a special emphasis on improving outcomes for patients who respond poorly to PD-1 inhibitors.

Christian has more than 20 years of experience in the international biotechnology industry. Prior to founding OBT, he held a number of positions of increasing seniority with Oxford Glycosciences, and led the company's partnerships in oncology with Pfizer, GSK, Bayer, Wyeth, Takeda, Oxford University, UK, and the FDA.