

Unlocking the Potential of Checkpoint Inhibitors – The Challenge for the Next Decade

Immunotherapy is an exciting weapon against cancer but many patients fail to benefit. Scientists are increasingly focused on maximising the potential of the immune system for everyone, perhaps in combination with one of the oldest cancer treatments: radiotherapy

Marisol Quintero at Highlight Therapeutics

Immunotherapy is revolutionising cancer treatment. Immunomodulatory agents affecting the innate and the adaptive immune system – cell-based therapies, such as tumour-infiltrating lymphocytes and chimeric antigen receptor Ts, together with oncolytic viruses and therapeutic vaccines – are all helping boost the body's natural defences to fight cancer, complementing conventional treatments such as surgery, chemotherapy, and radiotherapy.

A glance at the figures shows the extraordinary extent of global investment and innovation in the field. *Nature* has estimated that the number of immune-oncology drugs in development rose 91% in the two years to 2019 to almost 3,900, and identified more than 5,100 active trials in the clinicaltrials.gov database. Of these, it says two-thirds were evaluating compounds in the T cell-targeted immunomodulator class.

The rapid rise in activity is echoed in rocketing market growth. Acumen Research and Consulting recently predicted that the cancer immunotherapy market will be worth more than \$115 billion by 2026, a compound annual growth rate of more than 10% from 2019 – other estimates are substantially higher.

The first immunotherapy agent, IFN-alpha 2, was approved by the FDA in 1986, followed by IL-2 and BCG in the 1990s.

A more recent breakthrough was the approval in 2011 of ipilimumab (antiCTLA4 Ab), the first in a new class of immunotherapy agents known as checkpoint inhibitors. These are able to switch T cells on so that they can recognise and attack cancer cells. The impact and growth of checkpoint inhibitors has been huge. Merck & Co's market-leading Keytruda® posted a 55% increase in sales in 2019 to more than \$11 billion, while Bristol-Myers Squibb's OPDIVO® recorded revenues of \$7.2 billion last year alone.

However, despite the significant improvements that checkpoint inhibitors have delivered in cancers such as melanoma and non-small cell lung cancer, the majority of cancer patients still fail to benefit. Even in the best scenarios, including melanoma and lung cancer, the response rate for single agent checkpoint inhibitors is only between 20% and 50%. The majority of other tumour types do not respond to immune checkpoint therapy at all. Additionally, response rates in areas such as gastrointestinal cancers, breast cancer, sarcomas, and some genitourinary cancers have been stubbornly low.

Research and clinical efforts are, therefore, turning to ways of 'unlocking' the full potential of checkpoint inhibitors. Another worrying factor is making this work even more urgent; patients who are treated with chemotherapy are more likely to get infections. However, a survey of 100 oncologists in the

UK recently revealed that 46% believe resistance to antibiotics will soon make chemotherapy unviable, with cancer therapies becoming obsolete in the next five to ten years. The current coronavirus pandemic shows just how vital it is to maintain a fully functioning immune system.

Checkpoint Inhibitors

It's likely three areas will dominate work in broadening and deepening the impact of checkpoint inhibitors over the next decade. First, a focus on why some tumours never respond to treatment, or initially respond and later progress; second, the ability to turn so-called 'cold' tumours – which are insensitive to checkpoint inhibitors – 'hot', and therefore, visible to the immune system; and third, much greater emphasis on how immunotherapy can interact with one of the oldest available cancer treatments: radiotherapy.

So, how do checkpoint inhibitors work? In the most effective cases, they bring in to play the full potential of the body's immune system, releasing the brakes so that T cells can recognise and kill tumour cells. However, without T cells, checkpoint inhibitors are inactive. That is why tumours with few or no T cells don't respond to treatment.

In some cases, even when T cells are present in the tumour, they are tricked into failing to recognise tumour cells by a clever evasion mechanism – reducing the tumour's expression of MHC-1, which is responsible for presenting the antigens that induce an immune response.

Increasing the so-called trafficking of T cells into tumours and improving the ability of T cells to see and recognise tumour cells by boosting the expression of MHC-1 are key areas of current research. Overcoming the limitations caused by toxicity is another.

Here, we believe immunomodulators that are injected directly into the tumour have an important role to play. Different oncolytic viruses and Toll-like receptor agonists have demonstrated the ability to increase T cell infiltration and enhance the activity of anti-CTLA4 and anti-PD1 antibodies



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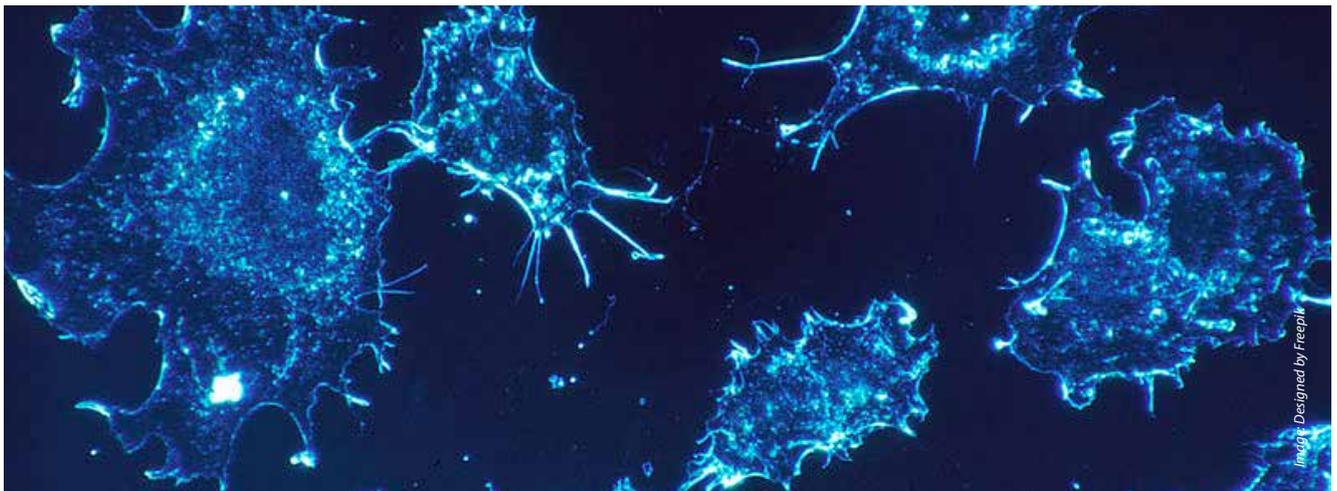


in the clinic. Emerging approaches include Amgen's T-VEC, Checkmate Pharmaceuticals' CMP001, and Idera's Tisotolimod. Technologies to deliver these agents directly into tumours are now being developed, potentially enabling greater use of these agents across different cancers.

Localised Approaches

Localised approaches, such as directly injecting into the tumour, are already demonstrating effectiveness in difficult settings such as the liver, which is the most common site of secondary tumours, or metastases, in gastro-intestinal cancers. Palliative, localised treatment of liver metastases has been shown to have a significant impact on improving survival in comparison to palliation without localised treatment. The presence of liver metastases has been correlated with poor clinical outcomes in patients treated with immunotherapy. In turn, the presence of T cells in the tumour has been linked to improved outcomes, reinforcing the idea that T cells effectively act like drugs.

There is interest in using localised immunotherapy to mount an effective antitumoural immune response. This is an area of high unmet medical need where currently there is a complete lack of consensus around treatment options, which can include radiofrequency ablation, chemoembolisation, microwave coagulation therapy, adjuvant chemotherapy, molecular targeted therapy, and palliative care.



Breakthroughs in intratumoural immunotherapies may help offer better treatment options for patients with metastatic liver disease and potentially many other cancers that don't respond – or respond poorly – to checkpoint inhibitors.

The other exciting part of the story is radiotherapy, which has played an essential role in the fight against cancer for more than a century. Around one in every two patients still receive radiotherapy as part of their treatment.

There have been a number of reports of non-irradiated secondary tumours regressing following conventional radiotherapy, both in combination with immunotherapy and without it. Up to now, we haven't really been able to understand the biological mechanisms behind the ability of radiation to affect non-irradiated metastases. There are theories that the most likely explanation is that regression of non-irradiated tumours is a consequence of the systemic activation of the immune system in irradiated tumour tissue. Radiotherapy can damage tumour cells, but it can also activate locally suppressive cell types. Targeting tumour-infiltrating myeloid cells to enhance the anti-tumoural effects of radiotherapy is another promising area of current research.

The interaction between radiotherapy and the immune system is being explored, with the aim of combining treatments that could have a greater clinical effect than any of the therapies used on their own. Multiple radioimmunotherapy (RIT) combinations are currently being assessed in early clinical trials. Potential uses for RIT include the treatment of prostate cancer, melanoma, ovarian cancer, lymphoma, high-grade brain glioma, and colorectal cancer.

So far, the vast majority of trials have tested the combination of localised radiotherapy with systemic immune therapies. However, recently, the idea of modulating the tumour microenvironment of irradiated lesions to enable systemic immune activation has also gained attention. Here, the combination of radiotherapy and immune therapy could work synergistically with systemic immunotherapies to achieve a more powerful clinical effect. At the moment, this area is being

explored mainly in academic trials, such as one at University of California Los Angeles, US.

Oncology has three major therapeutic focuses: medical, surgical, and radiation. Interventional oncology is a subspecialty of interventional radiology that deals with diagnosis and treatment of cancer. Medical oncology, by contrast, uses chemotherapy and other medications to treat cancer. Collaboration across different disciplines is essential to fully understand and maximise the potential synergies of these two treatment approaches, integrating RIT and precision medicine, so that novel treatment approaches can be designed based on tumour, immune, environmental, and patient-specific factors. The development of intratumoural immunotherapies, mainly administered by interventional oncologists, has the potential to connect these areas.

Although there is still a lot of work to do to achieve the goal of bringing the benefits of immunotherapy to many more patients, there is cause to be optimistic that the next decade will continue to deliver major breakthroughs in the treatment of a wide range of cancers.



Dr Marisol Quintero has been CEO of **Highlight Therapeutics**, formerly known as Bioncotech, since 2013. Marisol has significant experience in technology transfer and venture capital funded life-science start-ups.

She was previously Director of Innovation at the Spanish National Cancer Centre, Technology Transfer Manager at Fundación Botín, where she supported the successful launch of the companies Life Length and Axontherapix. Marisol has a degree in Pharmacy from the University of Valencia, Spain, and obtained a PhD from her research studies on metabolic changes triggered by hypoxia at University College London, UK, she also holds an Executive MBA from the Instituto de Empresa, Spain. Highlight Therapeutics is a private, clinical-stage company.