**Patient Stratification**

As new cases of cancer worldwide are set to increase by 70% over the next two decades, the race to find effective treatments has become more important than ever (1). Recent research has given novel insights into how the immune system fights cancer and how malignant tumours evade recognition through immunosuppression (2,3). This has led to the development of new immunotherapies that work by activating the body’s own natural immune defences, helping it to fight various cancers.

Immunotherapies typically fall into two main categories: active and passive. Active immunotherapies involve destroying cancer cells by strengthening natural immune defenses, often using a therapeutic cancer vaccine (4). One approach to cancer vaccination has been to extract tumour-associated antigens (TAAs) and inject them back into the patient in a suitable delivery vector, thus triggering the stimulation of the immune system to recognise and destroy the cancerous cells. Costimulatory adjuvants or immune modulators are also injected along with the vaccine in order to counteract the immunosuppressive environment induced by the tumour, enabling a strong and sustained immune response (5).

Passive immunotherapies do not directly weaponise the immune system, but instead aim to reduce or overcome the immunosuppressive effects of the tumour. Their primary goal is to reinstall the ability of the patients’ immune system to fight the disease. Many tumours secrete or carry proteins on their cell surface that can inhibit components of the immune system’s weaponry – like cytotoxic T cells for example. As such, this type of immunotherapy either blocks the silencer proteins expressed by the tumour cells, or targets their corresponding docking sites on the cytotoxic T cells, so that the two can no longer interact to suppress T cell activity (6). This is typically achieved by developing specific monoclonal antibodies that will bind to these factors. Checkpoint inhibitors are a well-known class of drugs that carry out this blocking function, side-stepping a key defensive tactic used by...
many tumours and enabling the patient's immune system to attack and destroy the cancerous cells (7).

**Great Potential**

So far, both active and passive immunotherapies have shown promise in human clinical trials, with some new drugs recently obtaining regulatory approval, stimulating further commercial and research interest (8). After the first proof-of-concept and FDA authorisation of a vaccine for prostate cancer, many subsequent cancer vaccine studies have demonstrated that they can be effective against other cancer types, including melanoma, breast, lung, pancreatic, colorectal and blood cancers, particularly during early-stage disease (9-11). For example, melanoma patients who responded to immunisation had longer overall survival times compared to non-responders – 21.9 versus 8.1 months – and patients with colon cancer had a 42% reduction in the risk of recurrence and/or death when given a cancer vaccine (12,13).

Checkpoint inhibitors show even greater promise when it comes to developing effective cancer treatments. These have significantly improved the prognosis of patients with certain types of cancers, such as advanced melanoma, bladder and non-small cell lung cancer (14-16). This has led to FDA approval and the rapid market penetration of several types of checkpoint inhibitor drugs. It is also reflected in the large number of trials currently taking place around the world (around 250, utilising over 40 checkpoint inhibitors).

However, due to the complex nature of the immune system and the huge molecular and morphological variability of the cancer cells it targets, both immunotherapies have significant limitations and risks that need to be addressed to drive further progress (7,17). One promising solution takes its inspiration from a precision medicine approach, using biomarkers as predictive tools to improve therapeutic outcome, better forecast and monitor success and reduce the chances of unwanted side effects.

**Hazards in Implementation**

While there is good evidence that active immunotherapies can be highly effective in cancer treatment, they are not without their risks. One important observation is that they can overstimulate the immune system, resulting in severe inflammatory responses and even the formation of autoimmune diseases (18). Consequently, a key challenge is to find a way to develop treatments that maintain the fine balance of the immune system, adequately stimulating it to target and destroy cancer cells while preventing unwanted immune attacks on normal cells (see Figure 1).

Checkpoint inhibitors, while a valued breakthrough in cancer therapy, do have some limitations. For example, as most of them are highly specific monoclonal antibodies, they target one type of molecule and are only effective on the small subset of patients for which this molecule facilitates tumour survival. This is significant, as the molecular mechanisms underlying any one type of cancer can vary a great deal among patients – even when the initial diagnostic methods used suggest they suffer from the same disease, so different drugs will likely be required to treat each subset (see Figure 2).

The monoclonal antibodies used as part of checkpoint inhibition strategies can also trigger so-called immune-related adverse events (irAEs), such as the joint changes typically seen in diseases like rheumatoid arthritis (19,20). In addition, checkpoint inhibitors cannot work on their own if the body fails to mount an adequate immune response, or if the tumour evolves so that it is no longer recognised by the immune system. As such, another issue is the improvement of treatment outcomes through the better use of combination therapies.
understanding of molecular mechanism behind each patient’s disease and prescribing the best medical approach to treat it.

**Autoantibodies as Biomarkers**

One approach that is showing great potential in resolving these challenges is the profiling of autoantibodies in individuals. These can be used as biomarkers of disease incidence, treatment progress and even as an early warning system for identifying autoimmune disease development. Although somewhat overlooked for this application until relatively recently, the inherent role of autoantibodies in the inflammatory response makes them excellent tools for improving immunotherapeutic drug development, informing patient selection in trials and driving treatment strategies in the clinic.

Autoantibodies are released by the body against TAAs, both naturally and after a vaccine is presented, and detecting the type and number produced can provide a wealth of useful information. For example, profiling could show whether a vaccine has effectively induced an immune response, or what subtype of cancer the patient is suffering from. As autoantibodies are often released in the early stages of cancer development – even without artificial stimulation from vaccines – profiling them in individuals can also help diagnosis and prognosis predictions (21). In addition, given that a pre-existing immune response can indicate a patient’s response to immunotherapy, profiling autoantibodies could help to preselect those patients who will respond, as well as explain the molecular causes of why some respond while others do not (22). The prolonged or over-expression of autoantibodies could also help to drive the formation of autoimmune disease, so detecting these in the patient would show if they were at risk of an adverse immune response during immunotherapy.

Profiling autoantibody biomarkers in cancer patients can also reveal significant clues about the specific molecular mechanisms underlying their body’s immune response, as well as their likely response to a particular vaccine or checkpoint inhibitor. In practice, this can provide several advantages to the cancer immunotherapy developers. For instance, autoantibody profiling could be used throughout clinical studies to reveal whether a particular drug is adequately stimulating the immune system. Moreover, it could help to quickly identify who is at risk of developing an autoimmune disease so that countermeasures can be initiated early on before severe adverse symptoms arise.

Given the clear advantages of profiling autoantibodies in driving forward effective and safe cancer immunotherapies, the creators of new treatments, regulators and investors require state-of-the-art biomarker screening technologies now more than ever.

**Looking Ahead**

The successful advancement of cancer immunotherapies will be at least partly reliant on profiling the biomarkers of individual patients to improve disease diagnosis and monitor for overstimulation. What is less clear is how this approach can be optimised. Certainly, the need for more effective biomarker strategies still exists. Precisely identifying patients who are most likely to respond to a specific immunotherapy, optimising assays to monitor tumour-directed immune responses and identifying biomarkers that allow precise monitoring and the prediction of adverse responses, are all now pertinent future research avenues in the progression of cancer immunotherapies (10).

Despite these unanswered questions, it is becoming clear that optimising cancer immunotherapies is likely to be based on a multiplex-multimodality approach in which different sources of biomarker data are detected using a range of assay methods – including DNA/RNA analysis, immunohistochemistry and...
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protein or metabolite measurements. One important type of biomarker will be autoantibodies, mostly due to their essential and prevalent involvement in the immune response. Given how unpredictable patient responses are to immunotherapies, autoantibody biomarkers will provide useful insights for ensuring their effectiveness, such as by preselecting patients who will be most likely to benefit, diagnosing early stage disease and monitoring irAEs.

Although cancer is still one of the leading causes of mortality worldwide, there is some hope on the horizon. Autoantibodies are set to have a starring role in helping to effectively weaponise the immune system by tailoring immunotherapies to work with the exact molecular makeup of precise groups of patients. As such, future research and technological advancements should take full advantage of autoantibodies as biomarkers in order to lead the way in developing ever more effective cancer immunotherapies.

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