Over the past decade, insights into the molecular mechanisms that cancer cells use to evade T-cells, antibodies/B cells and other adaptive immune defences have revolutionised oncology therapies. New understandings of how cancer evades innate immune defences – including macrophages, dendritic cells (DC) and Natural Killer (NK) cells – suggest a second, and perhaps even more significant, immunotherapy revolution may be at hand.

Recent preclinical and early clinical studies demonstrate that targeting molecular mechanisms that many cancer cells use to block macrophages and other innate immune cells from attacking may be effective against a wide range of cancers. Moreover, research suggests that therapies, which mobilise innate and adaptive immune responses, may be more effective when combined rather than used separately.

It is as though we have been fighting cancer with one hand tied behind our backs. Much as in boxing, where quick left-hand jabs open space for a decisive right-cross knockout, these studies suggest that a treatment plan that combines the two halves of the immune system work better than they do individually.

The opportunities for addressing unmet patient needs are profound, as are the commercial prospects for pioneers exploring this new immunotherapy frontier.

**Cancer in the corner: broadening immunotherapy targets**

The first wave of immunotherapies developed to treat cancer were monoclonal antibodies. These antibodies bind to antigens on the surface of tumour cells, such as HER2 on breast cancer, therefore inhibiting receptor signalling and marking cancer cells to be destroyed by the innate immune system. However, antibody therapy only works against cancers that display specific antigens, limiting their effectiveness.

The second wave of immunotherapies were T-cell checkpoint inhibitors that bind to molecules, such as PD-L1, and are responsible for creating an immunosuppressive microenvironment in tumours. Inhibiting these effects restores the responsiveness of tumours to T-cells. In doing so, T-cell checkpoint inhibitors can induce long-term responses in some patients with difficult-to-treat cancers, including melanoma, bladder cancer and non-small cell lung cancer.

However, T-cell checkpoint inhibitors do not work in all tumours. Also, since T-cell checkpoint inhibitors work by ‘taking the brakes off’ T-cells, they are only effective in patients who have a pre-existing activated T-cell response.

We are now in the third wave of immunotherapies, where treatments in development seek to integrate the innate and adaptive immune systems. Research shows that macrophages and other cells of the innate immune system help fight cancer in two major ways – and both potentially broaden and strengthen the body’s overall anti-cancer immune response.

First, innate immune cells recognise general patterns of abnormality and foreignness rather than highly-specific antigens. So they respond to, and
attack, a wider range of cancer cells than adaptive immune cells and antibodies. Second, innate immune cells can help the adaptive immune system better discover and destroy its specific targets in a variety of ways. These include:

- Macrophages and DCs, which can attract and activate cells of the adaptive immune system, including B- and T-lymphocytes, that, in turn, kill cancer cells.
- Macrophages and NK cells, which kill cells marked by antibodies produced by B-cells.

- Macrophages and DCs, which present antigens from cancer cells they kill that then activate T-cells against those cancer cells.

Evidence suggests combining innate immune modulators with established adaptive immunotherapies, such as tumour-targeted antibodies and T-cell checkpoint inhibitors, enhances the activity and longevity of treatments and may expand the population of patients who respond to immunotherapy (Figure 1).

As our understanding of the innate immune

References
6 Vyas, P, Knapper, S, Kelly, R et al. Initial Phase I Results Of The First-In-Class Anti-CD47 Antibody Hu5F9-G4 In Relapsed/Refractory Acute Myeloid Leukemia Patients. EHA Learning Center 2018; 214718.  
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system catches up with our knowledge of adaptive immune responses – and how the two work together – several modulators of the innate immune system are being advanced. These include toll-like receptor (TLR) agonists, which can activate innate immune cells, therefore causing them to secrete cytokines and interferons and, subsequently, recruit and activate adaptive T- and B-cells. However, such agents tend to be toxic when given systemically. Currently, TLR agonists are delivered locally via intratumoral injection and other strategies to target them specifically to tumours are being explored.

Other innate immune modulators, such as NK cell activators and checkpoint inhibitors, and macrophage checkpoint inhibitors, stimulate innate immune cells to attack cancer cells directly and activate adaptive immune responses. In the clinic already are macrophage checkpoint inhibitors that target CD47, a protein expressed by most cells in the body that binds with SIRPs on the surface of macrophages. It is a powerful ‘don’t eat me’ signal that helps macrophages identify host cells as healthy cells, preventing phagocytosis.

In normal physiology, macrophages detect the balance of CD47 ‘don’t eat me’ signals present on a cell membrane against ‘eat me’ signals indicating the cell is diseased or distressed. Phagocytosis is triggered when the ‘eat me’ signals overwhelm the ‘don’t eat me’ signals. This is one way damaged and diseased host cells are detected and removed, and is the typical mechanism for removing older red blood cells from circulation. Similarly, most invading organisms do not express CD47, enabling macrophages to immediately recognise foreign cells and attack.

However, many cancers, both solid and hematological, over-express CD47. This prevents macrophages from attacking cancer cells, even though they also display several surface proteins indicating distress. It is as though the over-expressed CD47 acts as a bright light, blinding the macrophage to the presence of ‘eat me’ distress signals.

Blocking CD47 on cancer cells with monoclonal antibodies allows macrophages to respond normally to the ‘eat me’ proteins that are also present on cancer cells, triggering phagocytosis. This process can be enhanced by supplying an additional ‘eat me’ signal through a tumour-targeted antibody such as rituximab. In addition to directly destroying cells by phagocytosis, macrophages and dendritic cells then present peptide antigens from the digested cancer cells to the adaptive immune system, activating T-cells against these tumour-specific antigens wherever they may be found in the body (Figure 2).

Below we review current research and present a preliminary pro forma analysis of the therapeutic and market potential of such a combined innate-adaptive immunotherapy approach, which has the potential to enhance therapy efficacy and efficiency, while reducing overall development costs.

Cancer on the ropes: current research supports innate-adaptive immunotherapies

Research shows that many, if not most, cancer cells employ CD47 to conceal themselves from macrophages. The two classes of innate checkpoint inhibitors in clinical trials are IgG4 monoclonal antibodies targeting CD47, and SIRPs-Fc fusion proteins, which also bind to CD47 on body cells. Since 2014, six developers have initiated 14 clinical studies, including eight Phase I and two Phase II studies testing CD47 antibodies, and four Phase I trials testing SIRPα-Fc fusion proteins.

IgG4 CD47 antibodies

Preclinical and early clinical studies have demonstrated the efficacy of CD47 antibodies against a range of cancers as a monotherapy and combined with adaptive immune therapies. The first and most advanced is HuSF9-G4 (SF9), which was engineered with a human IgG4 Fc domain isotype. In addition to blocking the CD47 ‘don’t eat me’ signal, the IgG4 Fc domain provides an additional ‘eat me’ signal via interacting with the Fc receptor on macrophages and facilitates phagocytosis of cancer and other abnormal cells. Yet, the IgG4 Fc domain has minimal affinity for NK cells and does not mediate complement dependent cytotoxicity. This is critical because antibodies with other Fc domain isotypes, such as IgG1, can stimulate innate immune attacks against normal tissues that also express CD47.

In preclinical testing, SF9 was broadly active against a wide range of hematologic malignancies including acute myeloid leukaemia (AML), non-Hodgkin’s lymphoma (NHL), cutaneous T-cell lymphoma, acute lymphoblastic anaemia, and multiple myeloma1, as well as solid tumours including breast, ovarian, colon, liver and brain cancers2-4.

SF9 clinical trials beginning in 2014 showed the treatment was well-tolerated, with manageable and mostly minor side-effects and initial efficacy against AML and solid tumours, without reaching a maximum tolerated dose up to 45mg/kg1-7.

Clinical trials of another anti-CD47 monoclonal antibody, CC-90002, began in 2015 after preclinical...
Immunotherapy studies showed activity against several tumors, including lenalidomide-resistant multiple myeloma, triple negative breast cancer and AML. An ongoing study is testing monotherapy and will expand to treat CD20-positive NHL patients in combination with rituximab (NCT02367196)\(^{10-11}\).

The main challenge with IgG4 CD47 antibody therapies include its effect on red blood cells, sometimes causing transient anemia. Some programmes have managed this anemia using a priming dose strategy that culls older red blood cells and stimulates production of additional red blood cells before initiating full-strength therapy\(^{12}\). One advantage to these therapies is the limited side-effect profile at high doses because they generally do not attack healthy host cells.

**SIRPs-Fc fusion proteins**

Currently there are three SIRPs-Fc fusion proteins in clinical trials:

The first, TTI-621, combines a wild-type human SIRPα that binds to CD47 with an active IgG1 Fc domain, which presents a potent phagocytic signal to effector cells. Preclinical trials demonstrated how TTI-621 stimulated macrophages to attack tumour cells preferentially to normal cells and slowed growth of AML and lymphoma xenografts. TTI-621 does not bind to red blood cells, though it does attach to leukocytes and platelets\(^{11}\). In Phase I trials that began in 2016, TTI-621 has been proven effective as a monotherapy and when combined with rituximab in treating diffuse large B-cell lymphoma\(^{14}\). However, toxicity limited escalation of the dose in humans above 0.3mg/kg. Further investigation of TTI-621 is now focused on local delivery by direct intra-tumoral injection\(^{15}\).

The second, TTI-622, combines a wild-type human SIRPα to a IgG4 Fc domain, avoiding normal tissue toxicities associated with IgG1. A Phase I dose escalation trial of TTI-622 is under way in patients with advanced relapsed or refractory lymphoma or myeloma with plans to expand into combination treatments with rituximab, anti-PD-1 antibodies and proteasome inhibitors (NCT03530683).

The final one, ALX148, is a fusion protein made up of 1) an engineered SIRPα domain with more than a 7,000-fold greater affinity for human CD47 than wild-type SIRP and 2) an inactive IgG1 Fc domain. In preclinical trials, given the inactive Fc domain, it did not cause anemia and displayed modest activity as monotherapy. But it was broadly active in xenograft models in combination with tumour-targeting antibodies, such as obinutuzumab, trastuzumab, cetuximab and anti-PD-L1 antibodies that provide an additional ‘eat me’ signal\(^{16}\). Clinical trials, in combination with pembrolizumab, trastuzumab and rituximab, are ongoing in advanced solid tumour and lymphoma patients\(^{17}\).

**Down for the count: a preliminary proforma analysis**

The therapeutic and market potential for combining...
innate and adaptive immunotherapies are immense and have the potential not only to expand the range of patients who can benefit from immunotherapy, but also to distinguish immunotherapy pharmaceutical companies from the rest of the competition.

The impact these combination therapies can have for patients is considerable. For instance, a Phase Ib/II study treated 22 patients with refractory B-cell NHL (previously treated with a median of four lines of therapy) with 5F9 and rituximab. Of these patients, 50% had an objective response and 36% had a complete response. Of seven indolent follicular lymphoma (FL) patients, 71% had an objective response, while 45% had a complete response. And objective responses were observed in 40% aggressive diffuse large B-cell lymphoma (DLBCL) patients with 35% having complete responses.

That is nearly double the objective response and more than four times the complete response for standard-of-care treatment for DLBCL in a large 2017 study, and betters a 2014 study of idelalisib for relapsed indolent lymphoma by about 40% for objective response and a whopping seven times for complete response.

Considering that about 70,000 new cases of B-cell NHL are diagnosed annually in the US, it has been estimated that there are approximately 11,500 DLBCL and FL patients that have received three or more previous treatments and are in grave need of new therapies. At an average annual cost of $150,000 for an effective immunotherapy, such as a PD-1 or PD-L1 inhibitor, that translates to a revenue potential of nearly $1.8 billion for a salvage therapy in DLBCL and FL alone.

It might be well worth the effort. And that is not even considering all the other indications a combined innate-immune therapy might generate. Using this approach could be applied to preclinical evidence in infectious diseases, cardiovascular diseases and fibrotic diseases.

In addition, companies can further differentiate themselves from competitors in the market by adding a combination therapy approach to their portfolios.

Indeed, a future where we could significantly increase the chances of a complete response in patients across indications could considerably boost the value of combined innate-adaptive therapies. In fact, the chances of a complete response could increase so much that restoring the one-two punch of the innate and adaptive immune systems could become the standard of care for new cancer therapies, which raises the question: Can you afford NOT to include innate immune-boosting therapies as part of your oncology development programme? A recent Nature publication indicates that in September 2018, there were 2,250 clinical trials ongoing with T-cell checkpoint inhibitors. Is it time to deploy those resources more broadly?