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New frontiers in immuno-oncology

Against the backdrop of a very deep and broad pipeline, the next breakthroughs in the immuno-oncology space will hinge on leveraging partnerships to improve existing therapies and to develop new strategies.

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Over the past few years, the rapid development of novel cancer immunotherapy approaches has fundamentally disrupted the oncology space. Immuno-oncology (I-O) has not only become a key component of cancer therapy, but has also reshaped priorities in oncology research and development (R&D) across the industry, and unprecedented clinical success in certain cancer types continues to fuel record investment and partnering activity. According to the American Association for Cancer Research, as of July 2018, there are more than 8,000 ongoing I-O trials and over 2,000 I-O agents, including checkpoint inhibitors, vaccines, oncolytic viruses and cellular therapies, in preclinical or clinical development. Moreover, for the past few years, I-O has been driving partnering in the oncology space—32 of the 35 multibillion-dollar oncology licensing deals inked between 2013 and 2017 are focused on I-O (BioPharma Dealmakers B3–B6, March 2018) and further major I-O deals have been signed in 2018 (**Table 1**).

The intense innovation activity in I-O has already yielded results. Last year saw the FDA approval of the first two chimeric antigen receptor (CAR)-T cell therapies, which target CD19 in B cell blood cancers, as well as two further drugs that inhibit the PD-1–PD-L1 (programmed cell death 1–programmed cell death 1 ligand 1) immune checkpoint in patients with solid tumors. However, although the clinical successes so far have been substantial, there are still many opportunities for improvement, including the development of strategies to identify and combat the multiple tumors that are not responsive to checkpoint inhibitors, and expansion of the capability of cell therapies to target antigens other than CD19, potentially also encompassing solid tumors. This article highlights how industry and academia are partnering to develop next-generation I-O solutions, boosted by the large volumes of funding flowing into the space.

Cold, cold, cold, warm … HOT!

Checkpoint inhibitors, which are the most widely investigated class of immunotherapies, act by 'taking the brakes' off the patient's immune system, enabling T cells to attack tumors. However, a big question regarding such interventions is the extent to which a tumor is susceptible to attack. This susceptibility, as it turns out, is a function of factors such as the extent to which a tumor is infiltrated by immune cells, especially by T cells, and of the mutational load of the tumor cells.

Broadly speaking, tumors with high levels of immune-cell infiltration and mutational loads—called 'hot' tumors—are likely to be responsive to checkpoint inhibitors, whereas those that have no or very low levels of infiltrating immune cells and low mutational loads are termed 'cold' and are generally nonresponsive to checkpoint inhibitors. While this conceptual framework is simplistic (and is rapidly evolving as our understanding of the complex factors that underlie tumor responsiveness improves), various approaches are already being developed to help transform cold tumors into hot tumors. Two strategies in particular—the use of oncolytic viruses to cause inflammation inside the tumor and the direct modulation of particular innate immune pathways—have triggered a wave of start-up formation, acquisitions and some early positioning of larger players in the field through R&D partnerships to test the novel agents in combination with checkpoint inhibitors.

> "I-O has been driving partnering in the oncology space"

For example, in February this year, Merck & Co. acquired the Australian oncolytic virus company Viralytics for $394 million. Another big pharma followed suit in May, when Johnson and Johnson's biotech arm Janssen Biotech acquired BeneVir, gaining a novel oncolytic virus technology and a number of preclinical candidates.The deal includes an upfront payment of $140 million and potential milestone payments of up to $900 million.

Also recently in May, Oncolytics Biotech entered into a clinical collaboration agreement with Merck & Co. and Northwestern University to test its intravenously delivered immuno-oncolytic virus, Reolysin, in a phase 2 clinical study for the treatment of pancreatic cancer in combination with Keytruda (pembrolizumab), Merck & Co.'s PD-1 inhibitor. Similar to other oncolytic viruses, Reolysin induces selective tumor lysis, triggering tumor inflammation and in turn the innate and adaptive immune responses.

At the R&D level, Transgene and BioInvent International started a collaboration in December 2017 to codevelop oncolytic viruses that encode BioInvent's anti-cytotoxic T lymphocyte protein 4 antibody in Transgene's engineered *Vaccinia* virus. The goal of the collaboration is to demonstrate the improved outcomes from treating tumors with an oncolytic virus that encodes a checkpoint inhibitor compared with a simple combination of the two agents.

Approaches to directly modulate the immune system in the tumor microenvironment are also gaining traction. One of this year's top partnerships—Pieris Pharmaceuticals and Seattle Genetics—is focused on the development of novel immune system-activating molecules that consist of a tumor-targeting antibody fused to the immune system-agonistic costimulatory protein anticalin. These antibody–anticalin fusion proteins are designed to activate the immune system preferentially in the tumor microenvironment. Last year also saw deals surrounding targets that modulate innate immunity, including stimulator of interferon genes (STING), the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome and retinoic acid-inducible gene 1 protein (RIG-I). In August 2017, Bristol-Myers Squibb acquired the biotech IFM Therapeutics for $300 million upfront and

Table 1 | Selected high-value immuno-oncology deals in 2018

Licensee or acquirer	Partner company	Date	Deal summary	Indication	Value ($ millions)
Celgene	Juno Therapeutics	January 2018	Celgene acquires Juno Therapeutics, including its clinical-stage CAR-T candidates JCAR017 and JCARH125	Cancer	9,000
Merck & Co.	Eisai	March 2018	Merck and Eisai partner to develop Lenvima as both a monotherapy and a combination therapy with Keytruda for multiple cancer types	Bladder cancer, endometrioid carcinoma, hepatocellular carcinoma, melanoma, non-small-cell lung cancer and renal cell carcinoma	5,755
Bristol-Myers Squibb	Nektar Therapeutics	February 2018	Nektar and Bristol-Myers Squibb collaborate to develop and commercialize NKTR-214 in combination with with Opdivo and/or Yervoy	Broad range of solid tumors and blood cancers	3,630
Kite Pharma	Sangamo Therapeutics	February 2018	Using zinc finger technology, Sangamo Therapeutics and Kite Pharma partner to develop and commercialize engineered cell therapies globally	Cancer	3,160
Allogene Therapeutics	Cellectis	April 2018	Allogene to develop and commercialize with Cellectis's allogeneic UCART programs	Cancer	2,800
Servier	Shire Pharmaceuticals	April 2018	Servier buys oncology business, including an early stage I-O pipeline from Shire Pharmaceuticals	Cancer	2,400
Eli Lilly	ARMO BioSciences	May 2018	Eli Lilly acquires ARMO BioSciences, including its phase 3 candidate pegilodecakin	Cancer	1,600
Boehringer Ingelheim	OSE Immuno-therapeutics	April 2018	OSE Immunotherapeutics and Boehringer sign partnership deal to develop and commercialize OSE-172 against advanced solid tumors	Solid tumors	1,389
Seattle Genetics	Pieris Pharmaceuticals	February 2018	Seattle to partner with Pieris to develop novel antibody–anticalin fusion proteins for solid tumors and blood cancers worldwide, using Pieris's anticalin technology	Hematological neoplasms and solid tumors	1,230
Janssen Biotech	BeneVir Biopharm	May 2018	Janssen Biotech acquires BeneVir Biopharm, its core T-Stealth oncolytic virus technology and its pipeline of oncolytic viruses	Solid tumors	1,040

Only 24 of the 103 deals reported in the first half of 2018 disclosed cash amounts. Source: Thomson Reuters Cortellis.

$2 billion in milestones, gaining preclinical candidates including STING and NLRP3 agonists. Shortly after, Merck & Co. paid $135 million upfront and $410 million in milestones to acquire Rigontec and its phase 1 RIG-I agonist RGT100.

Next-generation CAR-T cells off to the races

The first CAR-T cell therapy, Novartis's Kymriah (tisagenlecleucel) for the treatment of children and young adults with relapsed or refractory B cell acute lymphoblastic leukemia (ALL), was approved one year ago, followed soon after by Kite Pharma's Yescarta (axicabtagene ciloleucel) for the treatment of adults with certain types of non-Hodgkin lymphoma. Shortly before its approval, Kite was acquired by Gilead Sciences for $11 billion in one of the largest I-O deals to date. And in January this year, this was followed by Celgene's $9 billion acquisition of Juno, another CAR-T therapy pioneer.

Riding on the initial success of CAR-T cell therapies, researchers in academia and in industry are now racing to design novel CAR-T and other cell therapies that expand on their capabilities. One focus is pursuing novel antigens to target other cancers, including solid tumors, with a recent analysis of the cell therapy pipeline finding that more than 70 cell therapies with novel targets beyond CD19—including B cell maturation antigen, GD2 and human epidermal growth factor receptor 2—are now in clinical trials (*Nat. Rev. Drug Discov.* **17**, 465–466; 2018).

Efforts are also intensifying to develop off-the-shelf, allogeneic products that can bypass a key challenge of existing CAR-T cell therapies: the need to extract cells from a patient, engineer them ex vivo to express the required CAR construct and readminister them back into the patient. This autologous process is slow and expensive, and its success depends heavily on the health of the patient's immune cells.

To overcome this challenge, companies have been developing allogeneic CAR-T cell therapies consisting of healthy donor cells engineered to minimize any potential rejection due to human leukocyte antigen mismatch with the recipient. Allogeneic CAR-T cell therapies can be stored for off-the-shelf use and eliminate the need to create personalized therapy from a patient's own cells, simplifying manufacturing and reducing the time patients must wait for their treatment. A key component of developing these cells is the gene-editing platform used to alter the T cells, driving deals to secure access to these platforms through partnerships.

For example, in February of this year, Kite Pharma struck a $3 billion-plus deal with Sangamo Therapeutics for exclusive access to its zinc finger nuclease (ZFN) gene-editing technology. The ZFN gene-editing platform will allow Kite Pharma to accelerate the development of next-generation, off-the-shelf CAR-T cell therapies. And in April 2018, Allogene and Pfizer entered into an agreement for Allogene to develop Cellectis's UCART program—licensed by Pfizer from Cellectis and Servier—to treat CD19-expressing hematological malignancies. The lead asset in this collaboration is UCART19, which is in phase 1 clinical studies for ALL. A key component of this partnership, valued at $2.8 billion, is the access it provides Allogene to Cellectis's transcription activator-like effector nuclease gene-editing technology.

Celgene's Juno and Novartis already partnered as early as 2015 with Editas Medicine and Intellia Therapeutics, respectively, for access to those companies' CRISPR/Cas9 technologies. A third player in the CRISPR/Cas9 space, CRISPR Therapeutics, is developing CTX110 alone, an allogeneic anti-CD19 CAR-T cell therapeutic candidate, which could enter the clinic soon. The next year or so will be pivotal in determining how these partnerships pan out.

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