The year has got off to a fast start for oncology drug discovery, with numerous mergers, acquisitions and collaborations announced in quick succession. These ventures provide a window into key trends in oncology research, where investigators are likely to focus their efforts, and the tools and technologies that will enable pharmaceutical and biotechnology companies to turn promise into efficacious therapies.

Global spending on oncology therapies rose to $133 billion in 2017, with 63 new indications approved just in the five-year period from 2013 to 2017, according to the IQVIA Global Oncology Trends 2018 report. While the pace of innovation is accelerating, the challenges of increasing competition, pricing pressures and regulatory complexity are squeezing ROI. In this environment, collaborative efforts will play a pivotal role in advancing oncology drug discovery effectively and efficiently.

Several major ventures that are sure to impact the oncology landscape in the near and long-term were announced at the 37th annual J.P. Morgan Healthcare Conference in January. The largest was the Bristol-Myers Squibb (BMS) bid to purchase Celgene for a reported $74 billion, combining two successful oncology franchises – led by Opdivo® and Yervoy® from BMS, and Revlimid® and Pomalyst® from Celgene – along with early-stage pipelines that include drug candidates for solid tumor and hematologic cancers. In the meantime, Celgene has remained busy shoring up its oncology pipeline, announcing a partnership that allows it to license immuno-oncology candidates from Kyn Therapeutics, including an AHR (aryl hydrocarbon receptor) antagonist programme.

The J.P. Morgan conference also saw Eli Lilly announce an $8 billion bid to acquire Loxo Oncology, expanding Lilly’s capabilities into the field of precision medicine. Loxo focuses on highly-targeted therapeutics for genomically-defined cancers – those dependent on a single gene abnormality, detectable through genomic testing – and has TRK, BTK and RET inhibitor drugs in both the investigation and approval stages.

Early 2019 has likewise proven productive for GlaxoSmithKline (GSK) and Merck. The GSK acquisition of TESARO, completed in January, will accelerate its oncology drug discovery with the addition of TESARO drug candidate Zejula, a PARP inhibitor for ovarian cancer. In its announcement, GSK forecasted the potential to apply PARP inhibitors to a wider range of tumour types, with investigations under way for lung, breast and prostate cancer. Shortly after, GSK announced a partnership with Merck KGaA that could take immune checkpoint therapy to the next level for lung cancer treatment. The companies will jointly develop and commercialise a bi-functional antibody to target two immune checkpoint pathways – one involving PD-L1 and the other involving the transforming growth factor-beta (TGF-B) protein – which some patients with advanced non-small cell
lung cancer overproduce, promoting tumour growth. Additionally, the recent Merck bid to purchase Immune Design has the potential to advance cancer vaccine progress by combining Merck’s immune-oncology portfolio and pipeline with Immune Design’s two proprietary platforms (GLAAS® and ZVex®), designed to activate and expand the immune system’s ability to create tumour-specific cytotoxic T-cells \textit{in vivo}.

These ventures came on the heels of several major developments in the oncology space in late 2018, including Illumina’s pending acquisition of Pacific Biosciences – a move that should greatly advance the critical field of genome sequencing by combining both long and short-read genome sequencing technologies.

Partnerships such as these reflect some of the prime areas of focus for oncology investigators, as they build on initial successes and explore new treatment avenues. Unsurprisingly, it is evident that immunotherapy will continue to be a major emphasis.

**What is next for cell and gene therapy**
Within the immunotherapy arena, the growing field of cell and gene therapy is likely to benefit from collaborative efforts that can drive new innovations. Chimeric antigen receptor (CAR)-T-cell therapy – in which a patient’s own T-cells are genetically modified to target proteins expressed on a tumour – is one such example. The first approved CAR-T therapies (Kymriah® from Novartis and Yescarta® from Gilead) are indicated for hematologic cancers; as of this writing, no CAR-T therapies have been approved for solid tumours. With a goal of bringing this therapeutic option to a broader range of patients, a team of researchers in Sweden tested CAR-T therapy efficacy in melanoma. Engrafting xenografts in interleukin-2 (IL-2) transgenic NOG mice, in which the human IL-2 cytokine is expressed, they found CAR-T-cells were able to kill uveal and cutaneous melanoma \textit{in vivo} and \textit{in vitro}. The therapy proved effective even in patients resistant to adoptive cell transfer of autologous tumour-infiltrating T lymphocytes\textsuperscript{1}. The BMS-Celgene merger is but one example of a collaboration with the potential to enhance CAR-T therapy efficacy and expand its utility, given that Celgene has CAR-T drug candidates in various investigational phases.
Advances in gene editing also may drive CAR-T-cell therapy forward, as witnessed by the work of Cellectis. Its off-the-shelf CAR-T-cell therapy candidate (UCART123) uses gene edited CAR-T-cells as therapy for acute myeloid leukaemia and blastic plasmacytoid dendritic cell neoplasm, a rare blood cancer.

Though T-cell-based therapy can be effective in some instances, it is associated with risks such as neurotoxicity and cytokine release syndrome. It also has limitations; for instance, a patient already immuno-suppressed from a first-line treatment may not have sufficient T-cells to modify or stimulate. These drawbacks have spurred investigation into the use of NK (natural killer) cells in novel immunotherapies, since NK cells, unlike T-cells, can recognise and kill cancer cells with a reduced risk of cytokine storm or GvHD (graft versus host disease).

Effective NK cell therapy investigation will require relevant animal models capable of supporting sufficient NK cell uptake. A study presented at the 2018 Association for Cancer Research Conference demonstrated the utility of humanised mice engrafted with peripheral blood mononuclear cells (PBMCs) as relevant models for studying human NK cell biology. Investigators compared immune system reconstitution in several models, including an hIL-15 NOG mouse model (a superimmunodeficient mouse that expresses human IL-15 cytokine) and conventional NOG mice. hIL-15 NOG mice engrafted with human PBMCs demonstrated significantly greater human NK cell reconstitution as compared to conventional NOG mice and survived for seven weeks post-engraftment without signs of GvHD, providing a suitable study window.

While early studies have demonstrated the potential efficacy of various cell and gene therapies, safety risks remain a concern. When administering a live drug (in the form of cells) to treat cancer, those cells themselves may have a risk of tumorigenicity; both CAR-T and NK cells are potent in this regard. In an effort to limit tumorigenicity risks, Bellicum Pharmaceuticals has developed a first-of-its kind molecular switch. If a cell-based therapy demonstrates tumorigenicity, this switch can be activated to kill the administered cells. Innovations such as these will help to make cell and gene therapy increasingly viable immunotherapies by addressing known safety risks.

**Improving on checkpoint inhibitors**

Many of the recent advances in immuno-oncology have involved checkpoint inhibitors, including the
breakthrough PD-1 inhibitors pembrolizumab (Keytruda®) and nivolumab (Opdivo), as well as PD-L1 and CTLA-4 inhibitors. This antibody-based therapy binds to immune-checkpoint proteins expressed on a tumour or on T-cells, enabling the cytotoxic T-cells to target and kill the tumour. The first Nobel Prize in Medicine awarded for cancer therapy, in 2018, recognised the checkpoint inhibitor research of James P. Allison and Tasuku Honjo – a testament to the groundbreaking nature of this therapeutic approach.

The broad utility of checkpoint inhibitors across multiple tumour types has been well-validated both in the clinic and in the lab, including in-mouse models that have a humanised immune system coupled with either human tumour cells or patient-derived xenografts (PDXs). Since immunoncology depends on the ability to discern how tumours interact with immune cells within the host and the tumour microenvironment, such models have proven highly effective tools for assessing checkpoint inhibitor efficacy. In addition, syngeneic models – in which a mouse tumour is implanted in an immunocompetent mouse – are facilitating checkpoint inhibitor study by elucidating how immune cell subsets, cytokines or T-cell responses impact tumour growth and how the immune system regulates tumour progression.

As effective as current checkpoint inhibitors have proven in the lab and in a subset of cancer patients, they are non-efficacious in others. In many cases, it is believed that multiple immune checkpoint pathways are at work simultaneously, so inhibiting a single checkpoint is only partially effective. To overcome this, researchers have explored combining more than one checkpoint inhibitor to determine if synergistic benefit can be achieved in a broader number of patients. Despite the promise of this approach, a key limitation occurs in preclinical development, where the experimental new drug must be tested in the context of the fully humanised monoclonal antibody primary drug. Since the primary is human specific, and the new drug may or may not be, the rodent system must harbour compensatory genetic modifications. One way that researchers are overcoming this hurdle involves essentially humanising a mouse model twice: once to humanise the primary antibody target binding site, and again to humanise the experimental new drug target binding site. Scientists are genetically modifying mouse models in this way to enable studying the interactions between checkpoint inhibitors in a living system with a fully intact immune system. Once the molecular drug targets are humanised, the model can then be subject to syngeneic tumour xenograft studies for testing each drug alone and in combination for tumour killing efficacy. This model generation approach is beginning to see traction and has the potential to aid the many pharmaceutical and biotech companies partnering to advance and improve on checkpoint inhibitor therapies.

A growing trend in oncology research, and particularly in lung and breast cancer studies, is the use of relevant biomarkers to predict treatment efficacy, guide treatment selection and monitor outcomes.

**Greater human NK cell reconstitution was achieved in hIL-15 NOG mice engrafted with human PBMCs versus conventional NOG mice. The hIL-15 NOG mice survived seven weeks post-engraftment without signs of GvHD.**
post treatment. More than one-third of oncology trials were using biomarker-based immunotherapy as of late 2017, according to the IQVIA Global Oncology Trends 2018 report. In concept, biomarkers are small and large molecule signatures that can be used to determine whether a drug has a likelihood of success in a given patient. Biomarkers are obtained from patient biological samples, mainly blood and biopsies, and then analysed for an individual patient. Healthcare professionals then use biomarker profiles to make treatment decisions.

On the furthest (and most expensive) end of the biomarker spectrum is the use of PDXs in a mouse model, making the mouse an avatar in which to test the efficacy of a therapy tailored to an individual based on the unique make-up of his/her tumour. Champions Oncology, a US-based contract research organisation, employs a similar approach, developing custom PDX models based on highly specific characterisation of tumours and tumour subtypes. While there is significant potential for this work to improve clinical decision-making, a current drawback is that no mechanism for coverage under traditional health insurance exists as of yet, and broad implementation thus far has been limited due to cost prohibitions.

The case for cancer vaccines

Using vaccines for disease prevention or treatment is another emerging area of focus in oncology, encompassing off-the-shelf vaccines and those tailored to an individual patient’s genetic make-up. Typically, cancer vaccine development requires extensive screening to identify unique tumour antigens and then further engineering them for efficient presentation to the adaptive immune system via major histocompatibility complex (MHC) proteins. Similar to checkpoint inhibition, a key limiter in leveraging animal models for efficacy testing requires genetic humanisation to ensure appropriate downstream activity and function. In humans, the MHC machinery is known as the human leucocyte antigen (HLA) programme. HLA and MHC function similarly in mice and humans, but have diverged through evolution, leading to subtle but meaningful differences in the way murine MHC and human HLA present antigens in vivo. Using mouse models that express HLAs, researchers have begun to study human response to antigens in vivo. In silico modelling typically is used first to identify the peptides that bind to target HLA supertypes; then in vivo immunogenicity is confirmed in HLA transgenic mice, followed by development of a vaccine that incorporates the appropriate epitopes.

Though the field of cancer vaccines is still relatively young, several early successes have been achieved in the clinic and the lab. Inovio Pharmaceuticals recently announced a second patient in remission from HPV-related head and neck cancer in a Phase I trial after treatment with a DNA vaccine and a PD-1 checkpoint inhibitor, while researchers from the Scripps Research Institute, working with other investigators, developed a vaccine that demonstrated efficacy in a mouse model of melanoma when combined with a PD-L1 inhibitor. Given the growing trend toward combination therapies, it is perhaps not surprising to see leading players such as BMS and Merck now collaborating on trials that combine established PD-1 checkpoint inhibitors with investigational cancer vaccines for a variety of tumour types.

In keeping with the precision medicine trend, cancer vaccines are likely to take a more personalised approach in the future. Already there is interest in exploring how machine learning could be used to assess where the greatest risk of cancer exists in a given class of patients, then tailoring a vaccine accordingly. For example, the Epstein Barr virus has been associated with certain forms of lymphoma, prompting researchers to investigate whether tumour cells that produce proteins associated with the virus could be targeted by a T-cell-based vaccine capable of killing cancerous cells.

The microbiome-cancer link

While the microbiome is often associated with diseases of the gut, mounting evidence indicates the microbiome plays a role in a wide range of diseases. Several investigations are under way to explore the potential link to cancer, including a recently-announced $25 million study funded by Cancer Research UK to investigate the connection between the microbiome and colorectal cancer. Fourteen investigators in six countries will use animal models and organoids to assess a potential relationship, while also examining the effect of colorectal cancer treatments on patient microbiota.

Several studies have already shown a link between the microbiome and various cancer types. New York University researchers demonstrated that the pancreas has its own microbiome capable of driving immunosuppressive conditions in a mouse model and increasing disease progression. When the KC mouse model of pancreatic oncogenesis was derived as germ-free, the mice were protected against disease progression. A combination of microbial ablation and treatment with a PD-1 inhibitor reduced tumour growth, indicating that manipulating the microbiome can both limit disease progression and enhance treatment.
Three studies in humans, published in *Science*, found variations in the gut microbiome compositions of patients who did or did not respond to checkpoint inhibitor therapy. In one of the studies, conducted at the University of Chicago, patients with metastatic melanoma who responded better to a PD-L1 inhibitor were found to have a higher number of eight bacteria. When the same PD-L1 blocker was administered to mice, it was only effective in those that received fecal microbiota transplants from responder patients, with five of the eight bacterial strains associated with anti-PD-L1 in the patients also found in the mice.

For most microbiome-related research, germ-free animal models serve as the requisite host. However, other tools and services are emerging to more fully support the exploring interest in studying how the microbiome may impact cancer progression and treatment. For instance, it is possible to take any genetically-engineered strain of a mouse model and rederive it as a germ-free model, combining a germ-free host environment with the unique genetics the investigator wishes to study. Performing custom microbiota associations with a genetically-engineered model is also becoming more common, providing a personalised approach to therapeutic investigation.

**Where AI might lead**

As the drug discovery world strives to improve study reproducibility and translatability, the field of artificial intelligence (AI) is highly likely to play a role in achieving these goals. The increasingly massive data sets involved in preclinical and clinical research – including data on the human genome, tumour genetics, the microbiome and therapeutic responses, among others – will necessitate more effective and efficient means of analysis, which AI can offer. Whether it is designing and developing more predictive and targeted animal models, determining a drug target with greater precision, or identifying new indications for existing therapies, the ability to model the necessary data can accelerate insights, better inform decision-making, and ultimately yield improved outcomes.

Precisely how AI will be applied to pharmaceutical research in general, and specifically oncology research, is still taking shape, with many potential avenues under discussion. Given that cancer is a multi-factor disease that rarely involves just a single genetic mutation, and the fact that combination cancer therapies are increasingly common, oncology may be a prime target for the application of AI. Over time AI could enhance investigators’ abilities to consider the many factors that can impact a cancer’s development and progression – including age, gender, geography and more – and how various therapies in combination might yield the best outcomes.

Collaboration will continue to be a hallmark of oncology drug discovery, with the potential to accelerate the pace of innovation, reduce time to market and improve study translatability. From immunotherapy, to vaccines, to manipulation of the microbiome, an improved understanding of cancer biology and treatment efficacy and safety will require combining technologies, capabilities and expertise in unique ways that will ultimately transform cancer treatment.

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**References**


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