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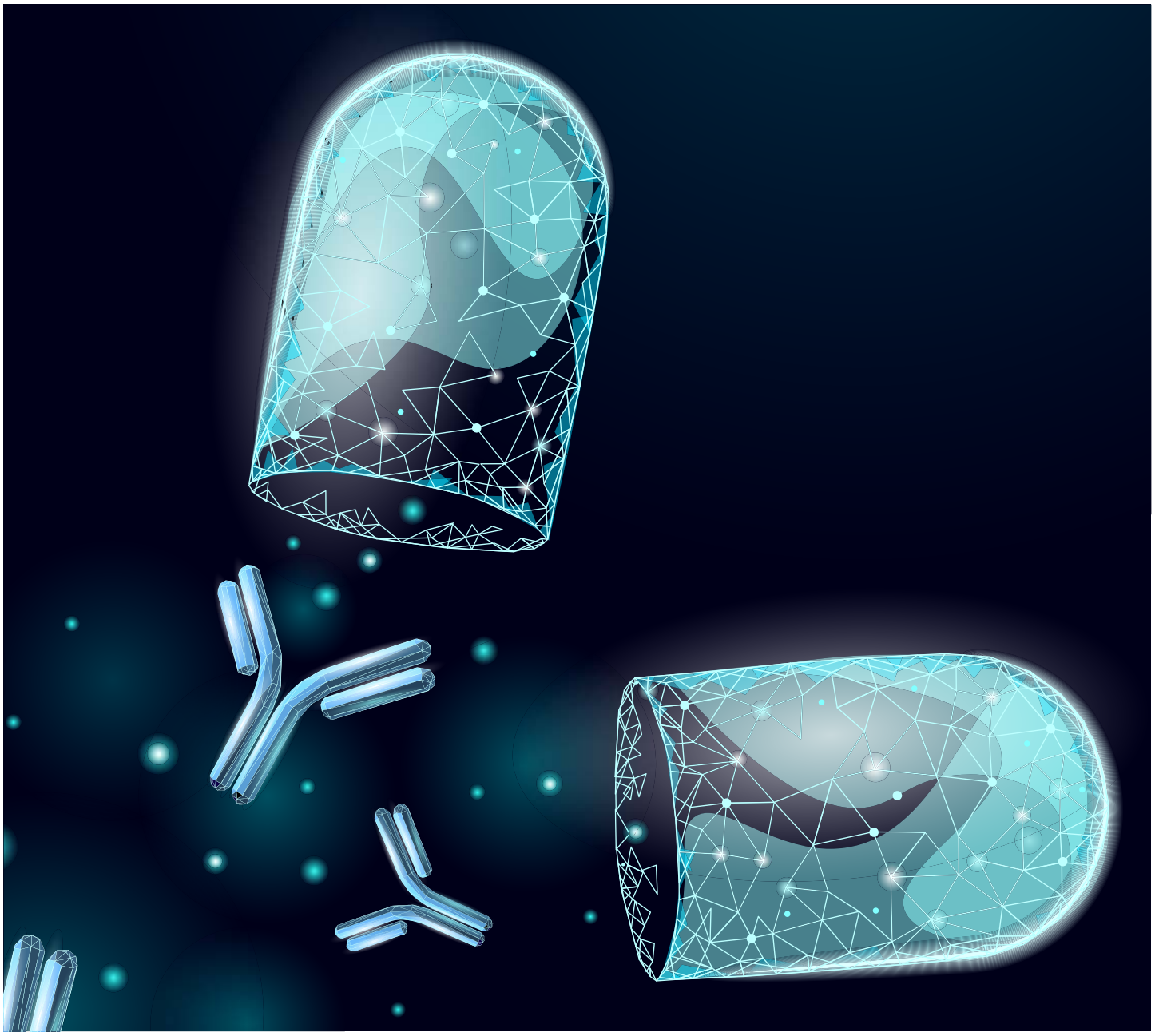

Immunotherapy: Where are the advances and breakthroughs?

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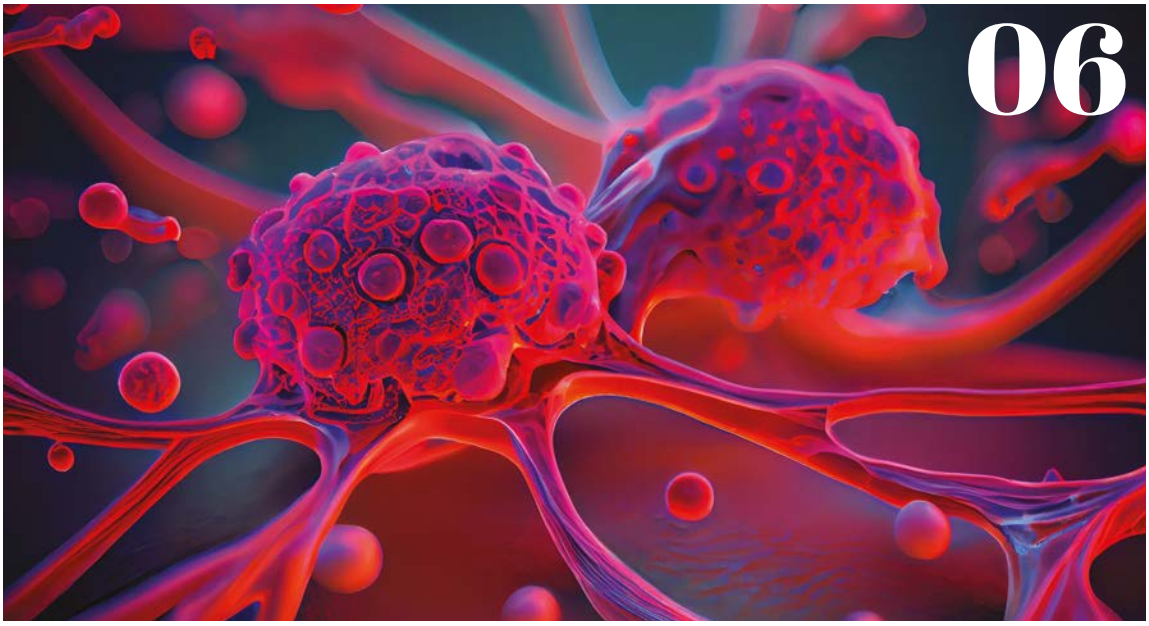

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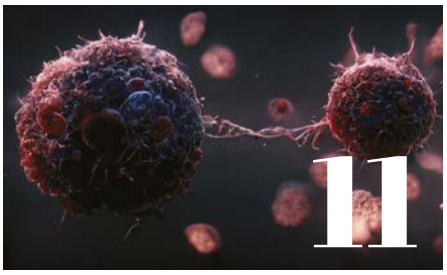

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Immunotherapy's promise

DDW Editor **Reece Armstrong** explores the burden of cancer and why immunotherapy represents an exciting approach to treat the disease.

Cancer has long remained one of healthcare's biggest challenges. This ominous disease represents one of the world's biggest burdens in terms of mortality and early loss-of-life, whilst at the same time putting undue strain on healthcare systems and the families affected by this disease.

Recent research in the British Journal of Cancer shows that in the UK, around 2 million years of life are lost to cancer each year. The study from Cancer Research UK and King's College London assessed the age at which cancer patients died from their disease and the general population's average life expectancy to estimate how many years are being lost due to cancer.

Cancers of the lung, bowel, breast, and those such as melanoma and liver had some of the largest totals of lost years due to their poor survival rates and high diagnoses each year. It's another study examining the impact that cancer has on lives and whilst the figures may not be surprising, they're a stark reminder that more work has to be done if progress is to be made into treating cancer.

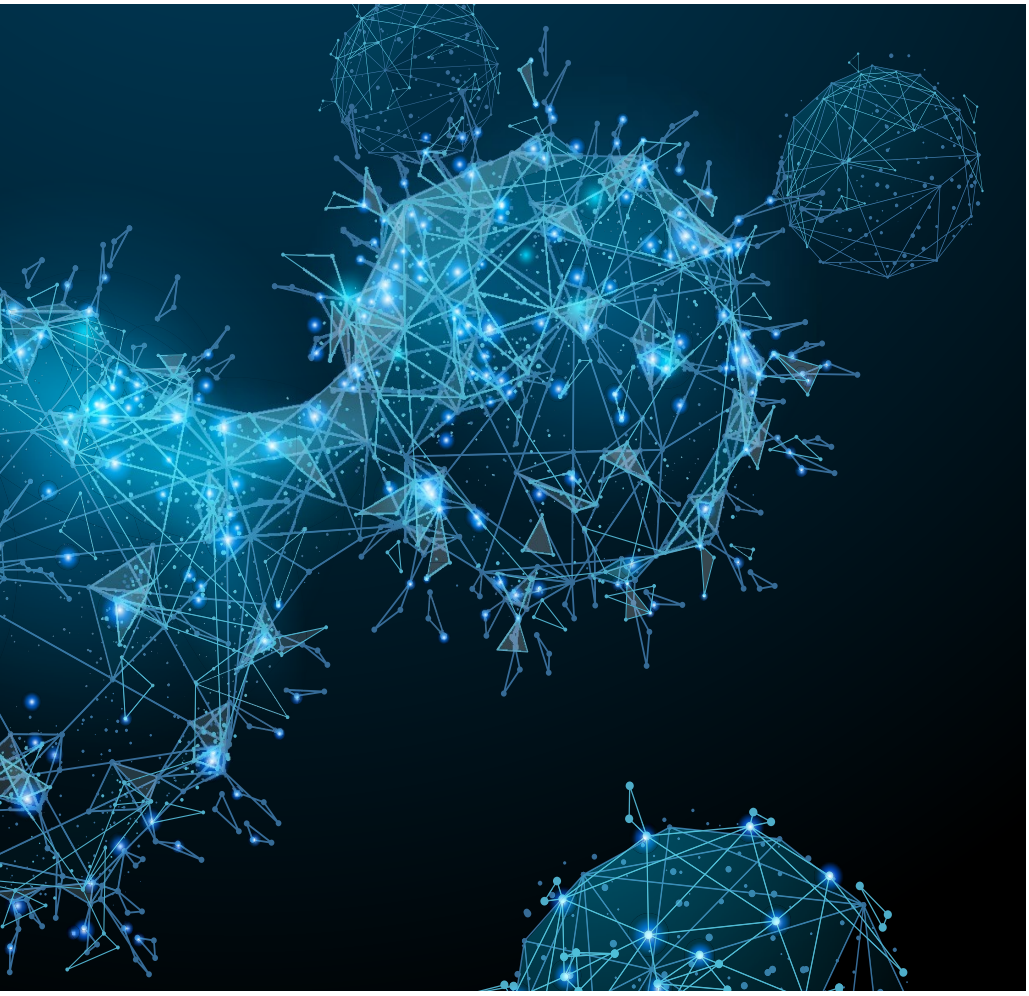
The study does highlight progress that has been made over the last 30 years. For instance, it references how the total number of years of life lost to cervical cancer has dropped from 43,600 to 21,800 since 1988. It also states that the rate of years of life lost for cancer has decreased by 15% since the 1980s, with the biggest decreases being in stomach, cervical and breast cancers.

Real progress then, but the industry is still chasing better treatments for cancer and immunotherapy has emerged as the favourite for many. It wasn't always like this. Whilst there are anecdotal reports of the relationship between tumours and the immune system referenced throughout Egyptian and Greek periods, the concept of immunotherapy can be traced back to the mid 1800s. Initial efforts to modulate the immune systems of patients to combat cancer were made by the German physicians Fehleisen and Busch who noticed patients' tumours shrank after they were infected with a type of skin infection known as erysipelas. Following this observation, the scientists independently began infecting cancer patients with erysipelas and started reporting further regressions in tumours.

Jump ahead to 1891 and the American surgeon William Coley explored further work in the field and observed how the same infection resulted in long-term regression of a sarcoma. Foley began a project where he injected heat-inactivated bacteria into patients with inoperable cancer and over the years reported more than 1,000 patients who had experienced regressions and even cures in their sarcomas[1]. Coley's methods never gained widespread acceptance at the time due to a number of reasons such as a lack of reproducible results and the use of radiation therapy and chemotherapy which, whilst not cures, did offer a level of reliable treatment.

Treatments for cancer have seen various iterations throughout the years but over the past decade or so immunotherapy has excited researchers around the world due to its potential. The promise of immunotherapy is that it can help the body's immune system attack cancer cells by itself and in some circumstances without the need for other forms of treatment such as chemotherapy or radiation therapy. Indeed, this could lead to prolonged remission due to the immune's systems ability for remembering disease-causing antigens[1].

It must be remembered that immunotherapy isn't a miracle cure. Cancer is incredibly difficult to treat. Each cancer cell can have over 11,000



genomic mutations and understanding how to target these cells with therapies is something scientists have struggled with for years. Thus the need for new therapies. Fortunately, the amount of research into immunotherapies for new cancer treatments is impressive.

Earlier this year, investigators at the Icahn School of Medicine at Mount Sinai reported findings for an RNA-based strategy that activates dendritic cells to eradicate tumours and prevent recurrence.

Findings from the study, though only in mouse models of melanoma, suggest that this approach could be effective against tumours that have already spread to other parts of the body and against different cancer types.

> **Fortunately, the amount of research into immunotherapies for new cancer treatments is impressive.**

Cancer cells can switch off various stages of the cancer-immunity cycle - the process by which dendritic cells educate T cells to kill the cancer cells. It's this immunosuppressive environment that impedes the activation of cancer-killing T cells, thus allowing tumours to grow.

"Most approaches to boost this critical role of dendritic cells aim to increase the activation signals provided to dendritic cells when specific molecules on their surface bind to tumour cells. However, these have not been as successful in clinical trials as hoped. This is because tumours have a tendency to evolve in different ways to switch off each stage of the cancer-immunity cycle," said Yizhou Dong, corresponding author of the study, Professor of Oncological Sciences, and a member of the Icahn Genomics Institute and the Marc and Jennifer Lipschultz Precision Immunology Institute at Icahn Mount Sinai.

The researchers used lipid nanoparticles to deliver two mRNA therapeutics, discovering that this helped reactive the caner-immunity cycle. The researchers also tested the effectiveness of this strategy in mouse models of B cell lymphoma and discovered that it reduced tumours by 83%. They plan on starting early-phase clinical trials in patients as a next step.

With plenty of ongoing work the future is bright for immunotherapies. Hopefully this means that cancer becomes less of the burden that it currently is and less years of life are lost as a result.

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Immunotherapies: advancements in cancer care

DDW Editor **Reece Armstrong** takes a look at the market for immunotherapies, its challenges and the recent developments that have taken place.

In the last 10 years immunotherapies have emerged onto the pharmaceutical market as exciting and innovative treatments.

Largely targeting the oncology sector, immunotherapy treatments have been described as breakthrough or 'miracle' drugs, though the reality is that whilst these therapies have seen great successes, they are still limited to certain cohorts of patients and response rates vary between 15-20%[1].

However, whilst immunotherapies can be limited, their successes in patients, particularly those displaying certain proteins on their tumours, has been positive and pharmaceutical R&D as a result has increased massively into the area of immunotherapy.

The first immunotherapy, Bristol-Myers Squibb's ipilimumab, was approved by the FDA in 2011, after it represented what the company then called its mission of "developing and delivering innovative medicines that address unmet needs in patients with serious diseases."

In the years since, R&D into immunotherapies has skyrocketed and more treatments have emerged onto the market addressing a range of conditions, with many more being investigated. As of, 2023, the FDA has approved 11 immune checkpoint inhibitors and 35 combination immunotherapies to treat multiple cancers.

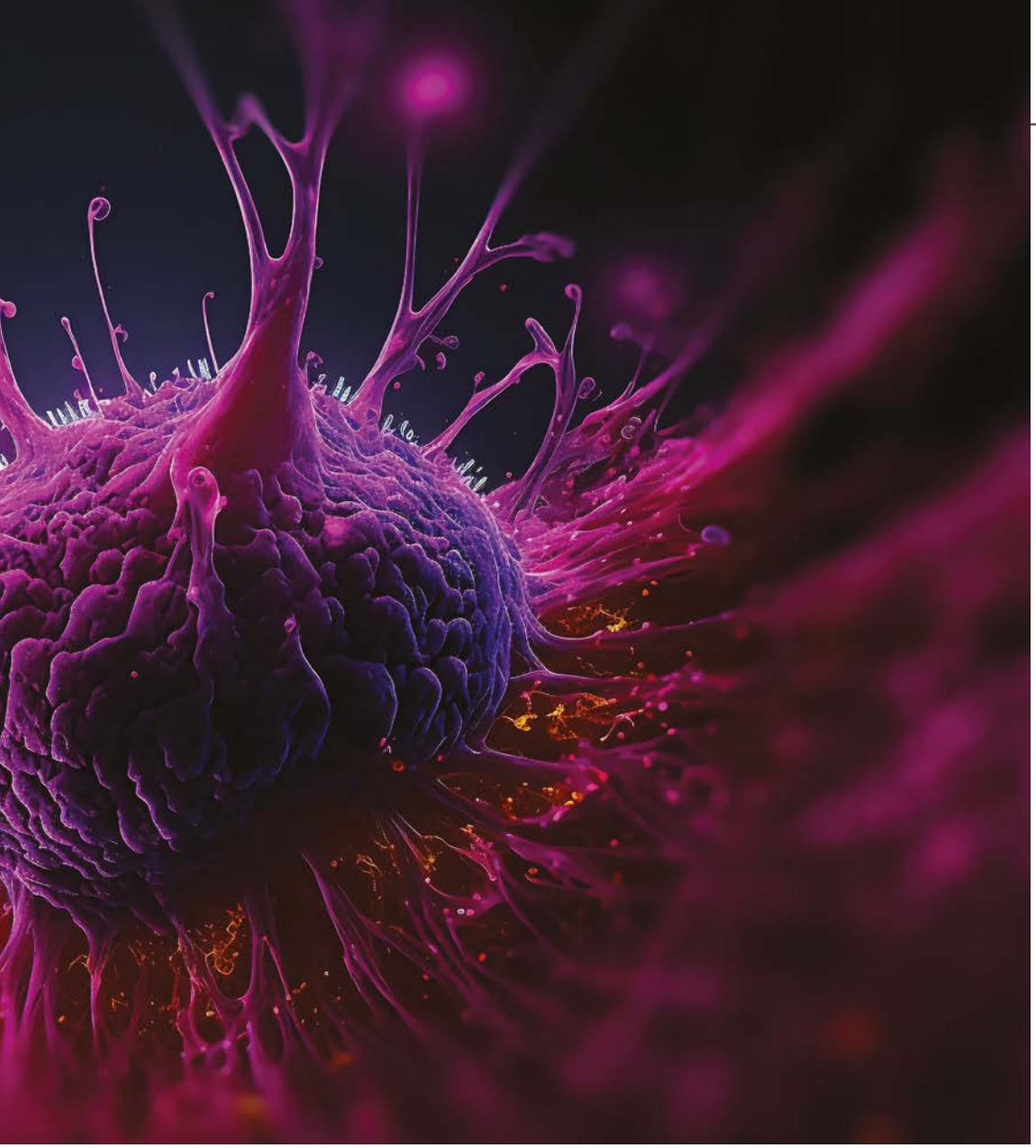
A significant moment in immunotherapy research came in 2017 when the FDA approved the ICI pembrolizumab for treatment of patients with solid tumours. The significance of the approval came from how pembrolizumab targets certain biomarkers on solid tumours making it an applicable treatment for a range of cancers. This approach differed from traditional methods to treat cancer which focused on a tumour's site of origin and is an example of a precision immunotherapy which helps a patient's own immune system target the specific molecular alterations of a tumour. This precision approach is something that has been followed by other therapies and treatments targeting biomarkers such as CTLA-4, PD-1/PD-L1, or LAG-3.

Challenges of immunotherapies

Genetic biomarkers

A recent Cancer Progress Report published by the American Association for Cancer Research[2] highlights the knowledge gaps that are currently limiting researchers' ability to predict patient response to immunotherapies.

To find out whether a patient will respond to an immunotherapy, clinicians use biomarkers to determine characteristics of a cell of a tissue. For instance, in the case of assessing patients for immune checkpoint inhibitors (ICIs), clinicians will look for the presence of surface level proteins such as PD-L1 alongside specific molecular



characteristics.

However, whilst the presence of certain proteins can inform a clinician whether a patient might respond to certain immunotherapies, concerns over the consistency of biomarkers such as PD-L1 between patients have been raised, meaning they may not make the most reliable of biomarkers for anti-PD-L1 therapies.

We can assume then that additional biomarkers are needed in order for clinicians to be able to ascertain which patients will respond well to immunotherapies. Immunotherapies have induced dramatic results in patients with cancer, however their efficacy hasn't been replicated outside of limited patient groups with a select group of cancer[2].

> **We can assume then that additional biomarkers are needed in order for clinicians to be able to ascertain which patients will respond well to immunotherapies.**

Reasons for this include limited biomarkers and cancer pathways, variability in cancer types and stages, along with the immunosuppressive biology of the cancer. For instance, the immunosuppressive nature of the tumour microenvironment (TME) has presented itself as one of the major challenges for immunotherapy treatments to be effective. In the TME, non-malignant cells are able to help tumour cells spread and metastasize, making immunosuppression a major driver of cancer growth in patients.

Diversity

A lack of diversity in genetic databases also means that knowledge of how tumours act within the body along with the immune system, is lacking in certain demographics. Studies have shown Black participants misclassified with cancers that have a high tumour mutational burden, meaning that they might not respond to certain immunotherapies have been designated to target specific biomarkers[3].

Expense

Drug development is a costly business and this is only exemplified with treatments like immunotherapies which can make up some of the most expensive drugs on the market. For instance CAR-T cell therapies have been estimated to reach over $500,000 in costs per patient. With these being targeted therapies that are developed using a patient's own cells to fight cancer, the development and manufacturing costs are higher than many other forms of treatments.

With costs for immunotherapies being so high there are issues with patient access for these drugs. In the US and other private healthcare sectors, high costs can mean that immunotherapies are inaccessible to certain patients. Even with insurance programmes covering certain FDA-approved treatments, co-payments can still be very high[4]. In places like the UK, access to immunotherapies can be limited due to healthcare systems weighing up the costs of the treatments versus the quality of life benefits these treatments can bring.

In 2018, NHS England struck a deal with MSD to make the lung cancer drug pembrolizumab available for routine use.

NHS England worked closely with MSD to reach a deal that would enable hospitals across England to use the cancer drug. Pembrolizumab, also known as Keytruda, was the first drug to break the new budget impact thresholds for products costing more than £20 million

a year. The NHS budget impact threshold is a new measure that allowed NHS England to negotiate prices with drug makers if new treatments are expected to cost more than £20 million a year.

NHS England and MSD agreed to a confidential agreement for reimbursement, allowing the National Institute for Health and Care Excellence (NICE) to recommend its use on the NHS. The drug would have cost around £84,000 per patient at its full price.

About the agreement, Meindert Boysen, Director of the NICE centre for health technology evaluation, said: "We have to make sure that any new treatment we recommend works well and is a good use of NHS resources. Recent changes to the CDF mean we have more flexibility in our process so we can grant early access to promising drugs whilst more data is gathered on their long-term benefits.

> **Drug development is a costly business and this is only exemplified with treatments like immunotherapies.**

"Pembrolizumab is one of the first new cancer drugs to benefit from this flexible approach and it can now be used routinely in the NHS. In the past 20 years there have been few improvements for people with this type of lung cancer so we are pleased to recommend routine access to pembrolizumab on the NHS."

Recent developments

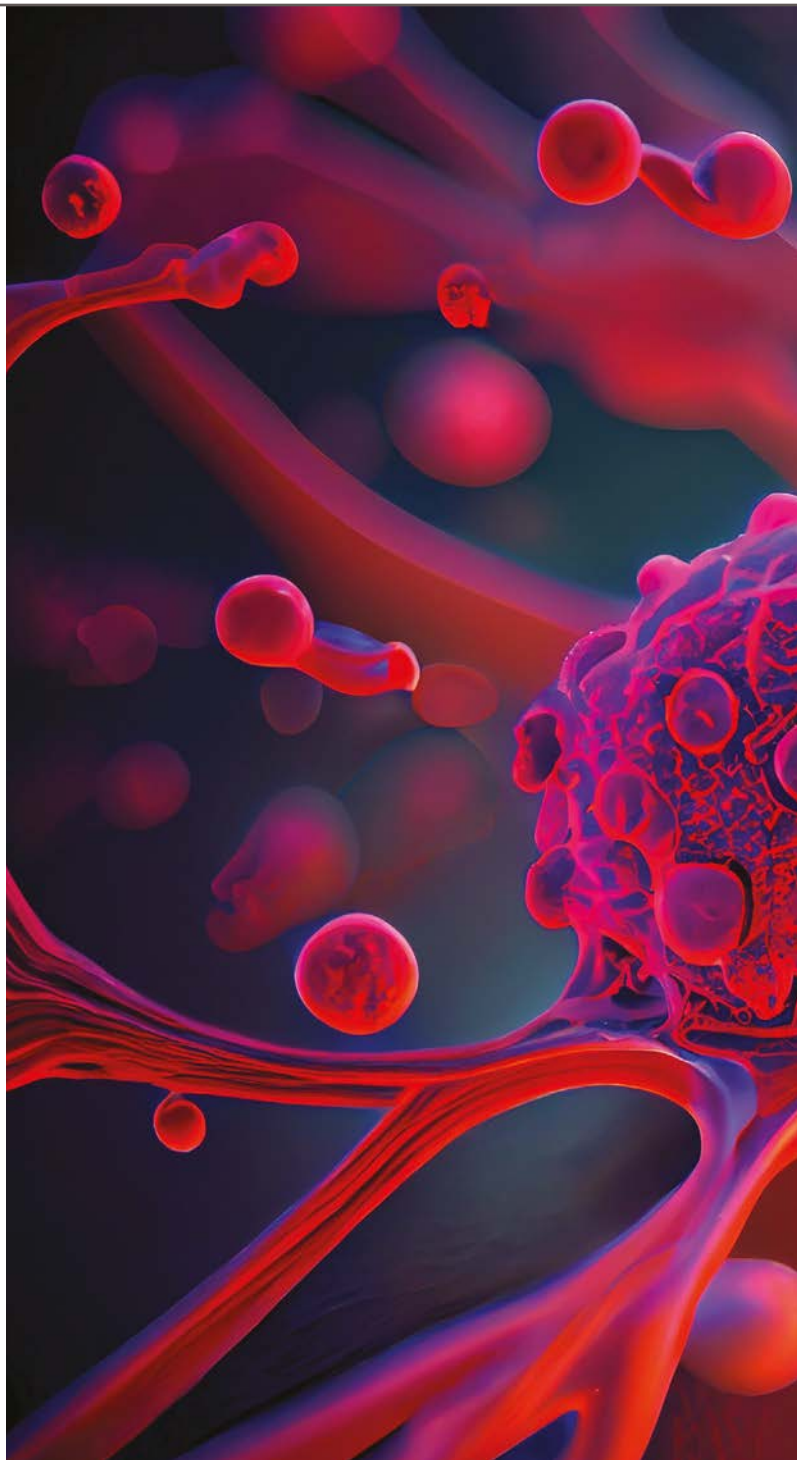
The world's first AI-designed bispecific T cell engager has been developed by the British biotech Etcembly, who is aiming to kickstart the next generation of immunotherapies with a pipeline of T cell receptor (TCR) therapeutics designed using generative AI.

Etcembly's lead therapeutic programme ETC-101 targets the validated antigen PRAME which is present in many cancers but importantly doesn't present on healthy tissue. ETC-101 is currently in lead optimisation and was advanced to this stage in 11 months, compared to over two years companies typically see with conventional TCR discovery and engineering pipelines.

The company is targeting further other areas in oncology and autoimmune diseases, including an immune engager targeting the MAGE A4 biomarker, which is present in cancers such as melanoma and non-small cell lung cancer.

The company has developed an AI engine that uses generative large language models (LLMs) to rapidly predict, design and validate TCR candidates. The engine scans hundreds of millions of TCR sequences then engineers them to achieve low pM affinity and eliminate cross-reactivity. This approach overcomes the barriers holding back the discovery and engineering of TCR candidates, accelerating the development of high-quality, potent and safe immunotherapies.

Over in the US, the FDA granted Orphan Drug Designation to 4SC's resminostat (Kinselby) for cutaneous T-cell lymphoma (CTCL). CTCL is a rare disease with approximately 5,000 patients being newly diagnosed in Europe each year. Currently, CTCL is incurable and treatment options for advanced-stage CTCL are limited. Patients do respond to current treatments, but these responses can be short-lived and less durable as the severity of the disease increases. One of the key challenges in advanced-stage

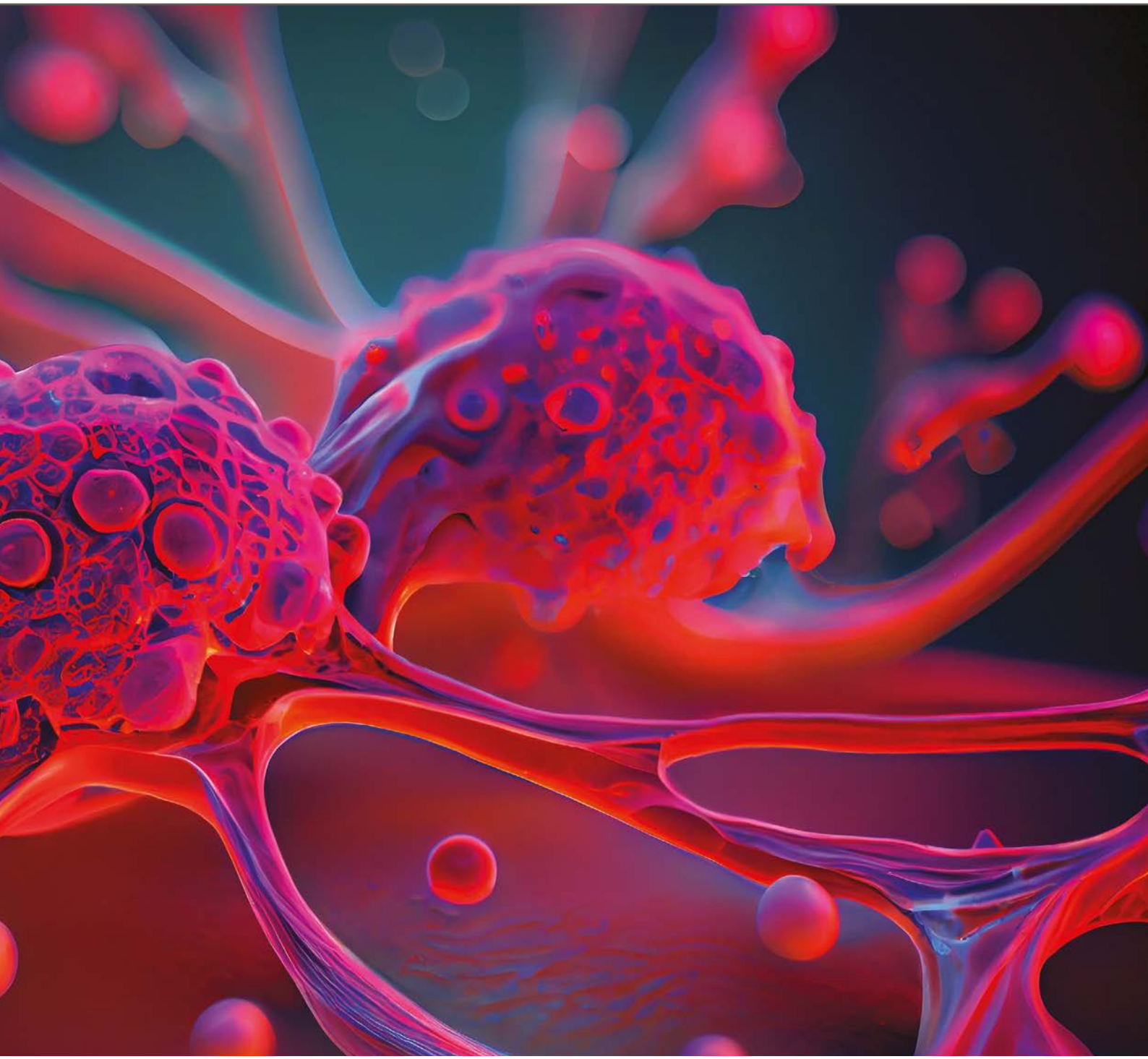


CTCL is to make remissions more durable by halting disease progression and improving patients' quality of life.

Resminostat is an orally administered class I, IIb and IV histone deacetylase (HDAC) inhibitor that potentially offers an approach to treating different kinds of cancer.

In a study, 4SC demonstrated that the drug is well tolerated can inhibit tumour growth and proliferation, cause tumour regression and strengthen the immune response to cancer.

Jason Loveridge, CEO of 4SC, commented: "Receiving orphan drug designation for resminostat provides us with a number of important benefits, most crucially seven years' market exclusivity in the US, a key foundation of our efforts to commercialise Kinselby. We are currently preparing a marketing



authorisation application for Kinselby in the EU, which remains on track for submission in Q1 2024."

Outside of oncology a new immunotherapy candidate could offer a more accessible and cost-effective alternative to current immunotherapies on the market.

Clinical trial data for Vaxxinity's UB-311 synthetic peptide-based drug show that it is safe and well-tolerated. UB-311 targets toxic beta-amyloid (Aβ) oligomers and fibrils and oligomers. Two monoclonal antiboides (mAbs) targeting Aβ have recently been authorised by the FDA, indicating that it's a valid target for disease-modifying immunotherapies of Alzheimer's.

In contrast, according to Vaxxinity, UB-311 offers lower rates of ARIA-E, less frequent dosing, and ease of administration through intramuscular injection.

Mei Mei Hu, CEO of Vaxxinity, commented: "Imagine expanding the addressable patient population of beta-amyloid immunotherapies by multiple orders of magnitude, potentially over 1,000x, and delivering life-changing medicine at a fraction of the cost. That is our vision for UB-311."

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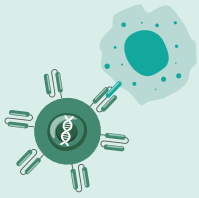

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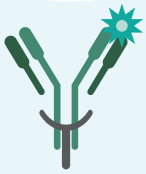

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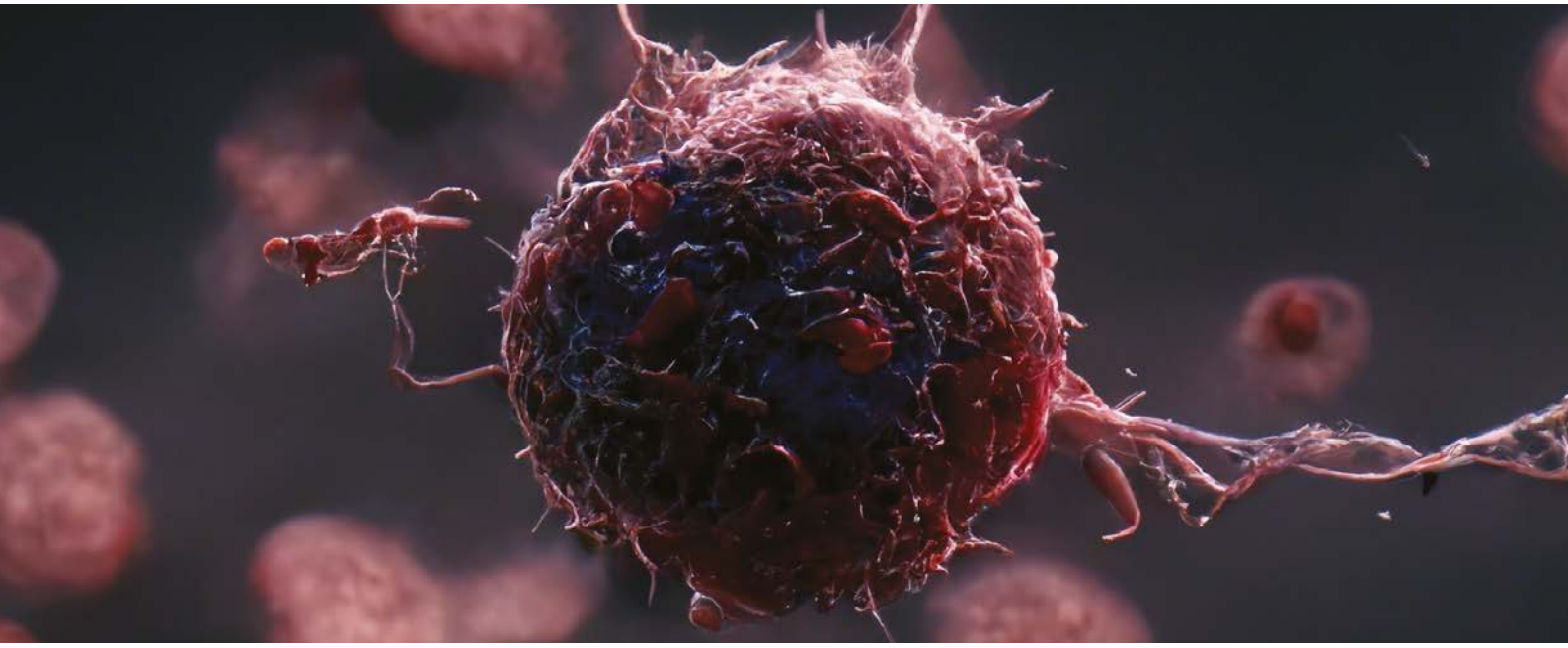
Immunotherapy is here to stay



DDW's **Megan Thomas** spoke with Frédéric Triebel, the French immunologist/oncologist who is best known for his 1990 discovery of the LAG-3 immune control mechanism. Triebel shares insights from his career, expands on his experience with the company he founded, Immutep, and comments on the future of immuno-oncology (I-O).

Background

Lymphocyte-activation gene 3, or LAG-3, is a gene that provides the genetic information to make a cell surface molecule with biologic effects on T-cell function. Triebel reported the first cloning of the LAG-3 gene in 1990.

Two years after this discovery, his team was able to show that the LAG-3 protein was a ligand for MHC Class II molecules like CD4. In 1997, the Triebel lab identified the LAG-3 amino-acid residues involved in LAG-3/MHC class II interaction. In 1998, Triebel et al. performed the first characterisation of the human CD4/LAG-3 gene locus, in the process identifying the LAG-3 promoter regulatory elements. Also in 1998, Triebel's team were the first to characterise the negative regulatory role of LAG-3 on CD3/TCR signalling. In parallel, his team was the first to show that, as a soluble molecule, LAG-3 activates antigen-presenting cells through MHC class II signalling, resulting in antigen- specific T-cell responses.

Triebel founded Immutep SA in 2001 to develop the clinical potential of LAG-3 and stayed with this company through to its acquisition by Prima BioMed in 2014. Prima BioMed rebranded as Immutep in 2017 and Triebel continues as Chief Scientific and Medical Officer of Immutep. Immutep, listed on ASX and NASDAQ, is a pure-play LAG-3 company, with five product candidates in development.

Pipeline

Immutep currently has three clinical, one pre-clinical, and one early-stage LAG-3 related product candidate under development. These include two antibodies for modulating immune responses in cancer and autoimmunity, which are being advanced through pharmaceutical partnerships with Novartis and GlaxoSmithKline. The company's lead product candidate is eftilagimod alpha (efti or IMP321), a first-in-class antigen- presenting cell (APC) activator currently being investigated in clinical trials as a treatment (in combination with chemotherapy or anti-PD-(L)1 therapies) for various cancer indications. The drugs in development are as follows:

- Eftilagimod alpha (efti or IMP321) – immunotherapy for cancer
- IMP761 – pre-clinical immunotherapy for autoimmune disease
- LAG525 or leramilimab (IMP701) – immunotherapy for solid tumours, blood cancer and breast cancer (partnered with Novartis)
- GSK'781 (IMP731) – immunotherapy in autoimmune diseases (partnered with GSK)

Triebel has had many landmark moments across his long career as an immunologist, one of which was being the lead author on the paper in 1990, LAG-3, a novel lymphocyte activation gene closely related to CD4. The LAG-3 receptor was a new concept at the time. Triebel and his team knew that T cells to be activated need two signals, signal 1 through the T cell receptor and signal 2 through co-stimulatory molecules like CD4, CD8 or CD28. A few days following T cell activation, T cells return to a more quiescent state, and T cell deactivation is also an active mechanism mediated by co-inhibitory receptors such as CTLA-4, PD-1 and LAG-3.

Looking back, looking forward

I ask Triebel to look back on those early days and comment on what the future looked like at the time. Are we on track, ahead, behind today compared to what the team expected at the time? Triebel recalls thinking, "it's now or never". At the time, nobody was interested in LAG-3, he says, so he committed to doing it himself through the founding of Immutep. This required convincing investors he was motivated enough, leaving the university, and building Immutep from the ground up. This period was difficult, with challenges such as the war in Iraq, as well as the fact that there was no real private money in France for a biotech venture such as this.

> **Looking forward, Triebel says that active immunotherapy is here to stay.**

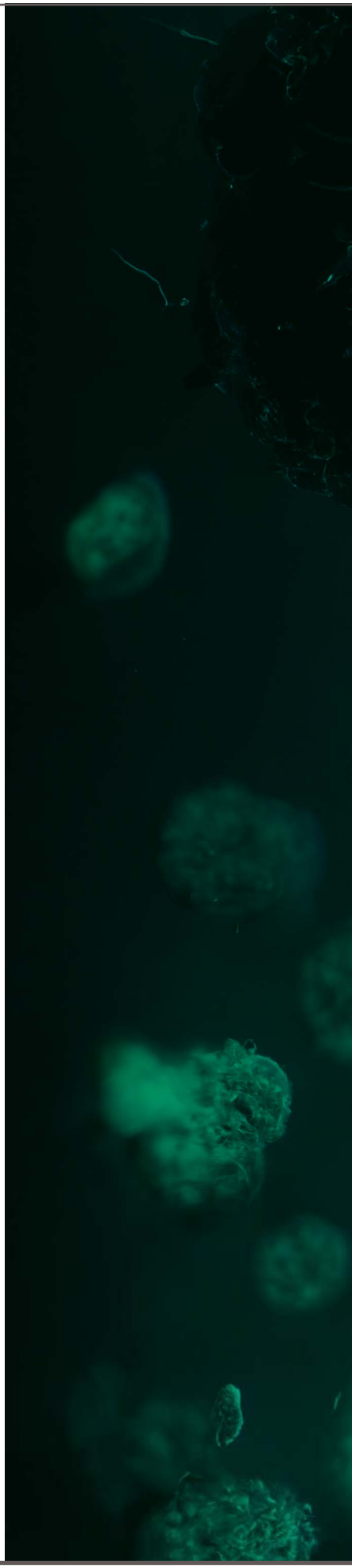
He says: "But, we did raise a few million, and we started going into the clinic not with a blocking antibody but with a very different, more innovative concept, which is a soluble LAG-3 protein, which is now eftilagimod alpha, as an immunostimulant. So, in 2005, we were already in the clinic. It was, at the time, a very small dosing – a few micrograms combined with an antigen, in other words, an adjuvant to a therapeutic vaccine. So, the idea was to activate the dendritic cells locally to increase antigen presentations to the T cells. Indeed, this worked as we had seen increased activated T cell numbers in the blood.

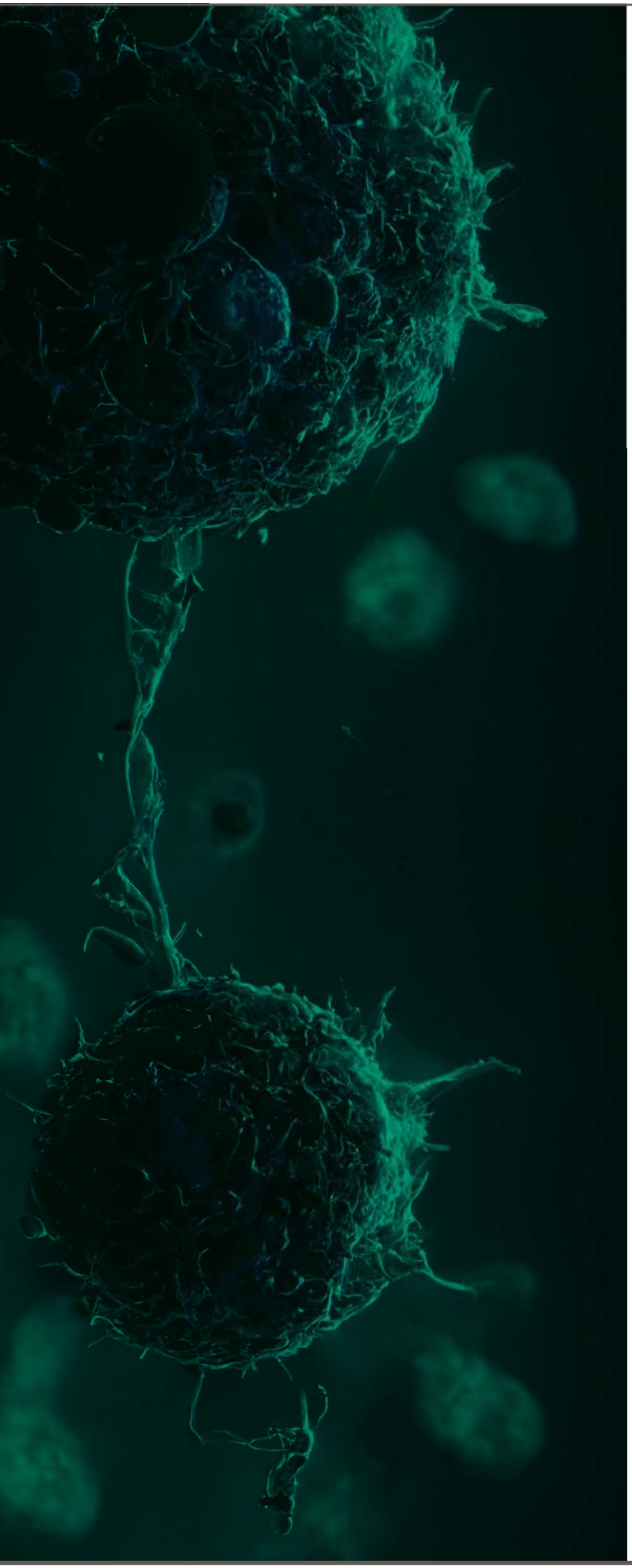
"The next step was to vastly increase the subcutaneous dosing to 30 mg efti in order to trigger the systemic activation of the dendritic cell network in the whole body. The first-in-man monotherapy trial studying our powerful antigen-presenting cell activator escalated efti dosing from 0.05mg to 30mg to treat advanced renal cell cancer, knowing that advanced cancer patients shed tumour antigens into the bloodstream continuously. We only treated patients for three months yet saw encouraging results and statistically significant increases in effector-memory CD8 T cells in all patients at higher efti dosing levels."

The breakthrough

So what was the point at which the cancer immunotherapy breakthrough started to feel real? Triebel says that 30 years ago, they were working with renal carcinoma tumours from metastatic patients and realised that there were as many T cells at the tumour site as tumour cells. It really looked like auto-immunity driven by T cells. Then they realised that there were two or three immunodominant clonotypes, i.e., T cells with the same T-cell receptor. That means two or three T cells have multiplied enormously. And why did they do that? He says: "Because there are two or three immunodominant peptides derived for instance from tumour oncogenes, that leads to clonotypic T cell proliferation."

So, the concept of immuno-surveillance is working in patients with metastatic tumours, and this is good news to see these patients with a 'hot tumour' environment (i.e., many activated T cells at the tumour site), even though this natural immuno-surveillance was not enough to stop the tumour growth. He says: "Back then, everything was about cancer vaccines trying to induce more T cells specific for the tumour antigens but then in 2010, oncologists realised for the first time that by blocking the CTLA-4 coinhibitory receptor, you induce autoimmune disorders





never seen before in oncology, as well as tumour regression in a fraction of the patients. Inducing de novo autoimmune disorders by strongly activated T cells, like thyroiditis, colitis, or pneumonitis in a few cancer patients, is indeed expected in the case of strong immunostimulation."

Around this time, the field of immunotherapy really broke through with the approvals of anti-CTLA-4 (ipilimumab) in 2011 and anti-PD-1 (pembrolizumab & nivolumab) in 2014. Then in 2015, nivolumab and ipilimumab became the first IO-IO combination to receive regulatory approval for melanoma.

Triebel saw an opportunity to synergistically combine efti with these checkpoint inhibitors, given its markedly different mechanism of action. Efti would push the accelerator on the immune response by targeting antigen-presenting cells, while checkpoint inhibitors would release the brakes on the immune system by targeting T cells. The clinical results to date in melanoma, lung cancer, head and neck cancer have been encouraging. He says: "Our enduring belief that targeting two different cell subsets would be very effective in fighting cancer continues to strengthen as efti has increasingly shown its ability to safely improve clinical outcomes for patients in combination with anti-PD-(L)1 therapies."

Looking forward

Triebel says that present I-O therapies is just the beginning of the story. He says: "We have treated the 'hot tumour' cancer patients, meaning the easy ones with a strong preexisting anti-tumour response at the tumour site. For patients with a lot of activated T cells producing interferon gamma at the tumour site, you'll just remove one break on the T cells, with an anti-PD-1 for instance, and that's enough for the T cells to eliminate a one kilo tumour mass disseminated at different anatomical sites. We have known for 50 years that T cells can do that – since the sixties. I mean, if you have Hashimoto's disease, in three weeks your thyroid gland will disappear. The same for the pancreatic islets in the case of type one diabetes. So, we know that T cells can kill organs, so why not tumours? This is an immunologist's view."

Looking forward, Triebel says that active immunotherapy is here to stay. With the success he has seen, he thinks that combining two I-O therapies in a chemo-free regimen for first-line or second-line treatment of metastatic cancers may help the majority of patients as long as one I-O is targeting dendritic cells like efti (to drive a broad immune response and an increase in activated T cells) and the other I-O is targeting T cells like anti-PD-(L)1 therapies (to remove the brake).

About the author

Frédéric Triebel, MD PhD, founded Immutep in 2001. He was appointed as Chief Medical Officer and Chief Scientific Officer following the acquisition of Immutep in December 2014 and joined Immutep's Board in 2022. Before starting Immutep, he was Professor in Immunology at Paris University. While working at Institut Gustave Roussy (IGR), a cancer centre in Paris, he discovered the LAG-3 gene in 1990 and in subsequent research identified the functions and medical usefulness of this molecule.

Precision cancer therapies: Where are we?

DDW's **Diana Spencer** reports on the recent Avacta Therapeutics Science Day, which explored the latest exciting developments in precision and targeted treatments for cancer and asked what advances the future might bring.

The Avacta Therapeutics Science Day brought together senior company scientists and international oncology experts to provide an overview of the current development of the company's cancer drug pipeline and the latest innovations in targeted oncology.

The speakers looked at the company's platform technologies, current pipelines, particularly AVA6000, and where targeted oncology might be heading in the next decade or so.

Dr Alastair Smith, CEO, began by stating the company's priorities: "In our therapeutics division, we are focused on innovative oncology treatments that make a genuine difference to patient's lives – both to their treatment outcomes and treatment experience. With our pre|CISION and Affimer platforms we have an unparalleled opportunity to develop really meaningful new cancer therapies, by developing targeted therapies, multi-specific immunotherapies, difficult to drug targets, and next-generation cell therapies."

Positive early signs for precision cancer therapies

In the first presentation, Dr Fiona McLaughlin, CSO, provided an update on Avacta's oncology candidates that are currently in clinical development. She explained the mechanism by which AVA6000 can provide more precise treatment than current chemotherapies. AVA6000 is a pre|CISION tumour-targeted form of the established chemotherapy doxorubicin; designed to limit cell penetration of the drug — and therefore its cell killing effect — until it is specifically activated by fibroblast activation protein α (FAP), which is in high concentration in many solid tumours compared with healthy tissues. The resulting reduced exposure of healthy tissues to free doxorubicin has the potential to significantly increase its therapeutic index by reducing the incidence of adverse effects, including cardiotoxicity and myelosuppression.

McLaughlin also revealed positive preclinical results for another pre|CISION drug candidate, AVA3996, a FAPα activated proteasome inhibitor, which has shown a flatline in melanoma tumour growth in mouse models. The company anticipates the drug will enter Phase I clinical trials in 2024.

Dr Andrew Saunders, Medical Advisor, followed this up with an update on the ALS-6000-101 Phase Ia dose escalation trial for AVA6000 currently being undertaken across various solid tumour types in heavily pre-treated metastatic patients. Early clinical data has shown a very favourable safety profile, with biopsies obtained from six patients across several cohorts demonstrating that the drug is preferentially being released in the tumour.

Although doxorubicin is the standard of care in this patient group, the current response rate is just 14-18%, so there is room for huge improvement.

T cell therapies for cancer: successes and challenges

Visiting speaker Dr Krishna Komanduri, Professor and Chief of the Division of Hematology

and Oncology at the University of California San Francisco, and a member of Avacta's Scientific Advisory Board, then provided an overview on progress in cell therapies.

Going through the timeline of advances in this area, he initially focused on leukaemia as a success story in stem cell cancer treatment, and how researchers realised T cells from stem cell donors were eliminating residual cancer but also brought the risk of graft versus host disease (GvHD).

We are now in an era of personalised immunotherapy with less focus on chemotherapy, and CAR-T cell therapy is one of the most exciting developments. The ZUMA-1 trial demonstrated the potential of CAR-T in large B cell lymphoma (with 40-50% of patients cured), justifying the treatment as second-line therapy in lymphoma. In myeloma, however, while the Ide-cel CGT therapy performed better than standard care in trials, it was but not curative and all patients relapsed within three years.

Komanduri asked why we see this failure rate and how we can we predict cell therapy failures, suggesting that this could be because living cells cease to circulate over time, cancer cells are able to mutate so that they no longer express the target, and that the patient's T cells may not be healthy after previous lines of treatment.

It is hoped that success in blood cancers can be translated in solid tumours, but in these diseases, scientists face the challenges of antigenic heterogeneity and a hostile TME. Komanduri suggested synthetic biology could increase efficacy of CAR-T cell therapy in the future. He also pointed out that less than 30% of patients in the US that qualify are receiving CAR-T cell therapies, emphasising that although manufacturers need to reduce the cost of these treatments, the focus from regulators should be on value rather than cost.

Current and future treatment strategies for soft tissue sarcoma

Dr William Tap, Chief of the Sarcoma Medical Oncology Service at the Memorial Sloan Kettering Cancer Center in New York, then took the lectern to offer insight to the audience on treatment strategies in soft tissue sarcoma.

He explained that the term describes a heterogeneous group of malignancies and is actually around 100 different diseases. Advances in genetic analysis is currently allowing greater understanding of the diseases and potential therapeutic approaches, and it is an exciting area to work in in due to the current unmet need and advances can go on to inform treatment of other cancers.

Doxorubicin, which was developed in 1973, is still the gold standard treatment for these patients, providing progression-free survival (PFS) of six months, overall survival (OS) of 19 months and an overall response rate (ORR) of 18%.

> **We are now in an era of personalised immunotherapy with less focus on chemotherapy, and CAR-T cell therapy is one of the most exciting developments.**

Tap examined the results of previous large trials for soft tissue sarcoma that failed and that led researchers to question whether the trials were being designed correctly. The approach then became much more targeted as they started to see success in small patient groups and trials started to focus on specific sub-types of patients with certain genetic mutations.

Through more targeted trials and an effort to improve understanding of the different diseases and how they impacted patients, there have been various successes in this area. Thanks to this approach and despite the challenges of securing regulatory approval due to small data sets and complex trial designs, 10 new treatments have been approved in last 10 years.

Targeted oncology 2030

The day concluded with a panel discussion on what the future of targeted oncology might bring over the next 10 years.

The panel expressed hope that immunotherapy will be available in more cancers than just blood cancers in the next few years, and that as our understanding of synthetic biology increases, this will escalate, and we will see much broader applications.

They also looked to a time when we have fully realised personalised medicine so we can apply the right drugs at the right time, and will be able to aim for cures in all cancers, rather than just extending life.

The impact of treatment on patients was also a large part of the discussion and the importance of realising that a one-size-fits-all approach won't work, as every tumour is so specific to every individual. The panel expressed hope that more predictable and less broadly toxic treatments will make a huge difference to patients' experience of treatment.

Tap developed this further: "Targeted oncology means developing a greater understanding of a patient's needs and how our therapies can help them. Patients will be empowered through greater knowledge to be able to take control of their disease and to help us understand what is important to them going forward and how the disease can be best managed and treated."

Where are the advances in treatments for triple-negative breast cancer?

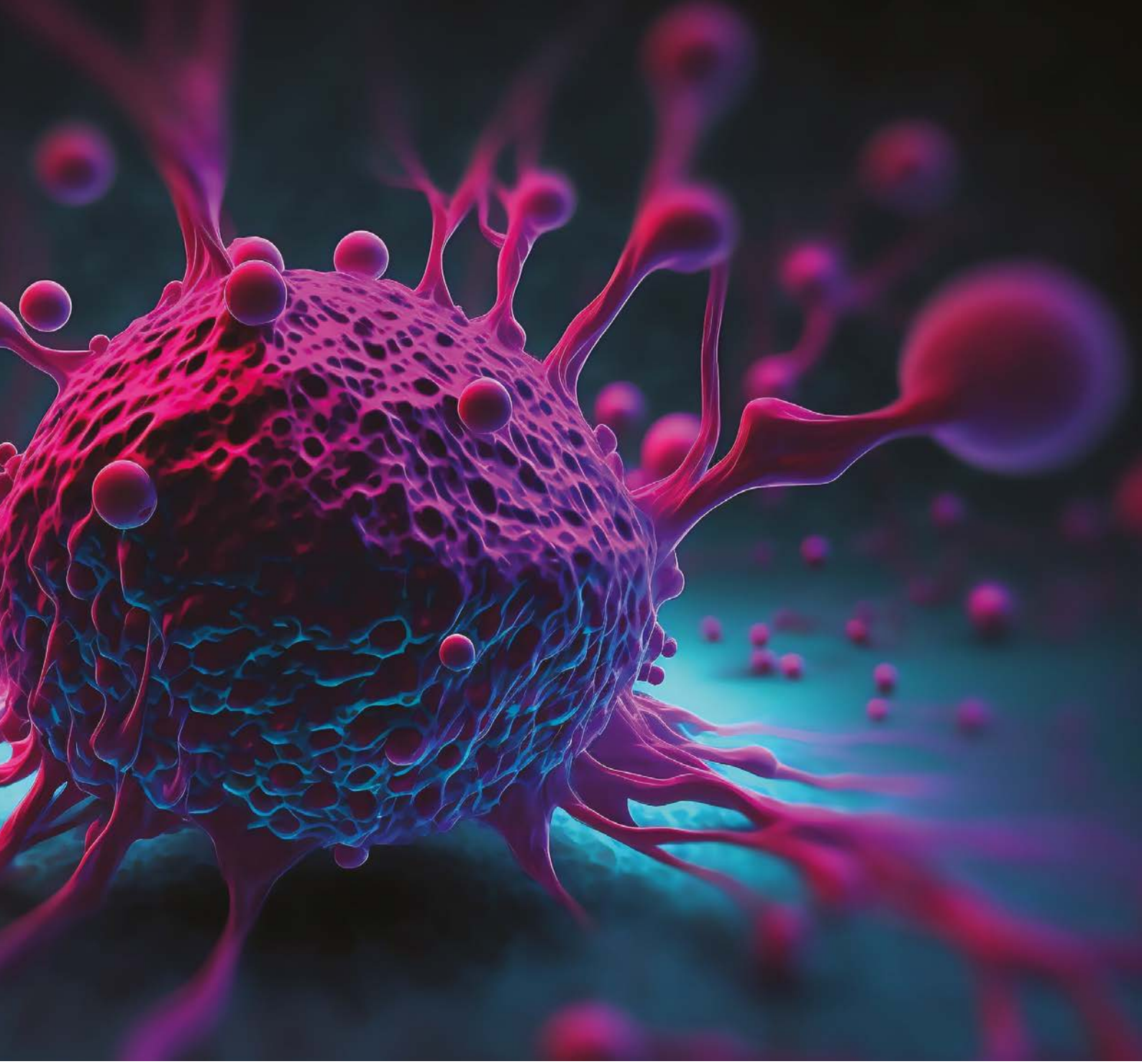
DDW's **Diana Spencer** investigates therapies in clinical development for triple-negative breast cancer and asks what future treatments might look like.

Triple-negative breast cancer (TNBC) accounts for approximately 15% of all breast cancer cases and is one of the main causes of death in women. However, because these cancers are not driven by any of the three molecules that can be blocked by targeted hormone receptor drugs, current treatment options are limited.

Standard therapy for early-stage TNBC is cytotoxic chemotherapy with carboplatin or docetaxel, though this approach is associated with significant side effects.

A recent study by researchers at The Institute of Cancer Research, London, has shown that certain characteristics within TNBC patients' primary tumours can predict how they will respond to different treatments after their tumours have spread around the body.

The researchers say that the presence of these biomarkers could be used to accelerate the development of more personalised treatments for TNBC. Though a positive step in the right direction, this is just a starting point. Are there



other treatments in the pipeline that could successfully target this difficult to treat group of cancers?

Combination therapy with pembrolizumab

In July 2021, the Food and Drug Administration (FDA) approved Merck's pembrolizumab (Keytruda) for high-risk, early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. The regulator had already approved the combination treatment in advanced cancers the previous year.

The FDA also granted approval to pembrolizumab in combination with chemotherapy for patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1. This was based on the results of the KEYNOTE-522 trial, which showed a pathological complete response rate of 63% for patients who received pembrolizumab in combination with chemotherapy compared with 56% for patients who received chemotherapy alone.

The addition of pembrolizumab was supported by further trial results in 2022. In the trial, KEYNOTE-355, overall survival improved only among patients whose tumours had relatively high levels of the PD-L1 protein – a PD-L1 combined positive score of at least 10. Among patients with this combined positive score, median overall survival was 23 months for those who received pembrolizumab and chemotherapy versus 16.1 months for those who received chemotherapy alone.

Despite the positive result, more than half of all patients with TNBC have PD-L1 combined positive scores of less than 10, so it was clear that more work was needed to find effective treatments for these patients.

Immunopheresis

In 2022, Immunopheresis was introduced as a new immuno-oncology option for advanced TNBC patients, both as monotherapy and adjunct therapy. As Immunopheresis

is a subtractive therapy that occurs outside the body, it is intended to be much better tolerated than chemo and immunotherapies, and used as an adjunct with these therapies, possibly in lower doses to reduce their toxicity.

Immunicom presented data from its ongoing clinical investigation at the American Society of Clinical Oncology's (ASCO) 2022 Annual Meeting, which showed that its Immunopheresis LW-02 Column helps spur upregulation of a patient's TNF-α pathway. 28 patients with advanced TNBC underwent 862 LW-02 Column Immunopheresis procedures. 10 patients received Immunopheresis LW-02 Column as a monotherapy, and 18 patients received it in addition to various chemotherapy regimens. After 30 minutes of therapy, the mean capture efficiencies for sTNF-R1 and sTNF-R2 – the proteins shed by tumours that suppress endogenous TNF-α – were 95.2% and 79.6%, respectively.

Commenting on the data, Immunicom Chief Clinical Officer Dr Victoria Manax, says: "LW-02 Column Immunopheresis data suggest that removing these factors is an increasingly promising modality for cancer patients. We continue to find evidence that this is an exciting new option in immuno-oncology."

Oncolytic virus treatment to stimulate the immune system

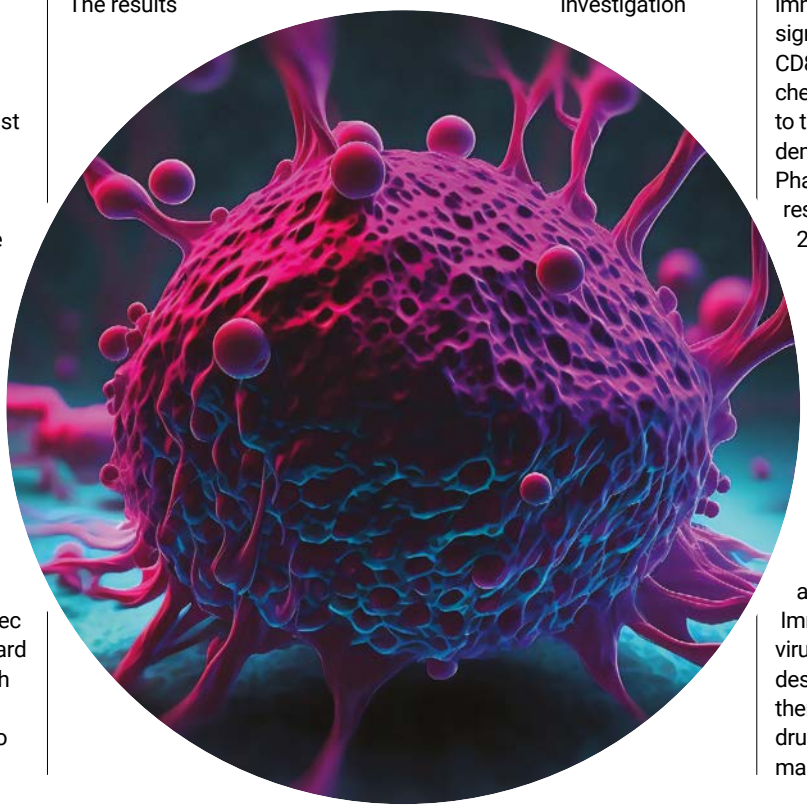
In February 2023, investigators at Moffitt Cancer Center in Florida shared results from a Phase II clinical trial of the oncolytic virus talimogene laherparepvec (TVEC) combined with standard chemotherapy in patients with early stage TNBC. Studies have shown that patients who have higher levels of immune cells within their tumours tend to have better responses to therapy, which suggests that agents that stimulate the immune system may be beneficial in TNBC.

TVEC is a modified herpes simplex 1 virus that includes coding sequences for the protein GM-CSF, which can stimulate the immune system. It is injected directly into the tumour and undergoes replication within the tumour cells, resulting in the breakdown of the tumour cell and production of tumour derived antigens. Immune cells can recognise the antigens, infiltrate the tumour and target the cancer cells for destruction. In addition, GM-CSF made by the virus acts as a beacon to help recruit immune cells to the tumour.

TVEC is approved to treat advanced, late-stage melanoma. The Moffitt Phase II trial was designed to assess whether the oncolytic virus also could be effective in combination with standard chemotherapy when given to TNBC patients before surgery. The results showed that 45.9% achieved a response, 89% of the patients remained disease free two years post-treatment, and no recurrences occurred in patients who achieved strong responses.

> **Triple-negative breast cancer (TNBC) accounts for approximately 15% of all breast cancer cases and is one of the main causes of death in women.**

"Our results demonstrate that TVEC, when added to systemic chemotherapy, may increase responses in high risk, early stage triple-negative breast cancer. There is evidence of robust immune activation within the tumour, and additional investigation of TVEC in combination with current chemoimmunotherapy for triple-negative breast cancer is warranted," concludes Soliman, lead study author, medical director of Moffitt's Clinical Trials Office and senior member of Moffitt's Breast Oncology Department.



LAG-3 immunotherapies

Later the same year, Immutep initiated AIPAC-003 (Active Immunotherapy, Eftilagimod Alpha, and Paclitaxel), an integrated Phase II/III trial to evaluate eftilagimod alpha (efti) in combination with paclitaxel for the treatment of metastatic HER2-neg/low breast cancer (MBC). Based on feedback from the FDA/EMA, the trial has been expanded to include (TNBC) patients.

According to the company, as a first-in-class soluble LAG-3 protein targeting MHC Class II ligands on antigen-presenting cells (APC), efti can improve clinical outcomes from standard-of-care chemotherapy. Its activation of APCs (e.g., dendritic cells, monocytes) triggers a broad immune response that includes significant increases in cytotoxic CD8 plus T cells armed with chemo-induced tumour antigens to target cancer. This was demonstrated in the AIPAC Phase IIb trial's encouraging results, including an over 2.9-month median overall survival improvement.

Conclusion

Treatments for TNBC have seen some progress in recent years, with the addition of pembrolizumab to standard chemotherapy offering hope to some patients. However, despite a number of promising new approaches in the pipeline, like Immunopheresis and modified viruses, this is still an area in desperate need of more targeted therapies and an opportunity for drug discovery innovation to make a significant impact.

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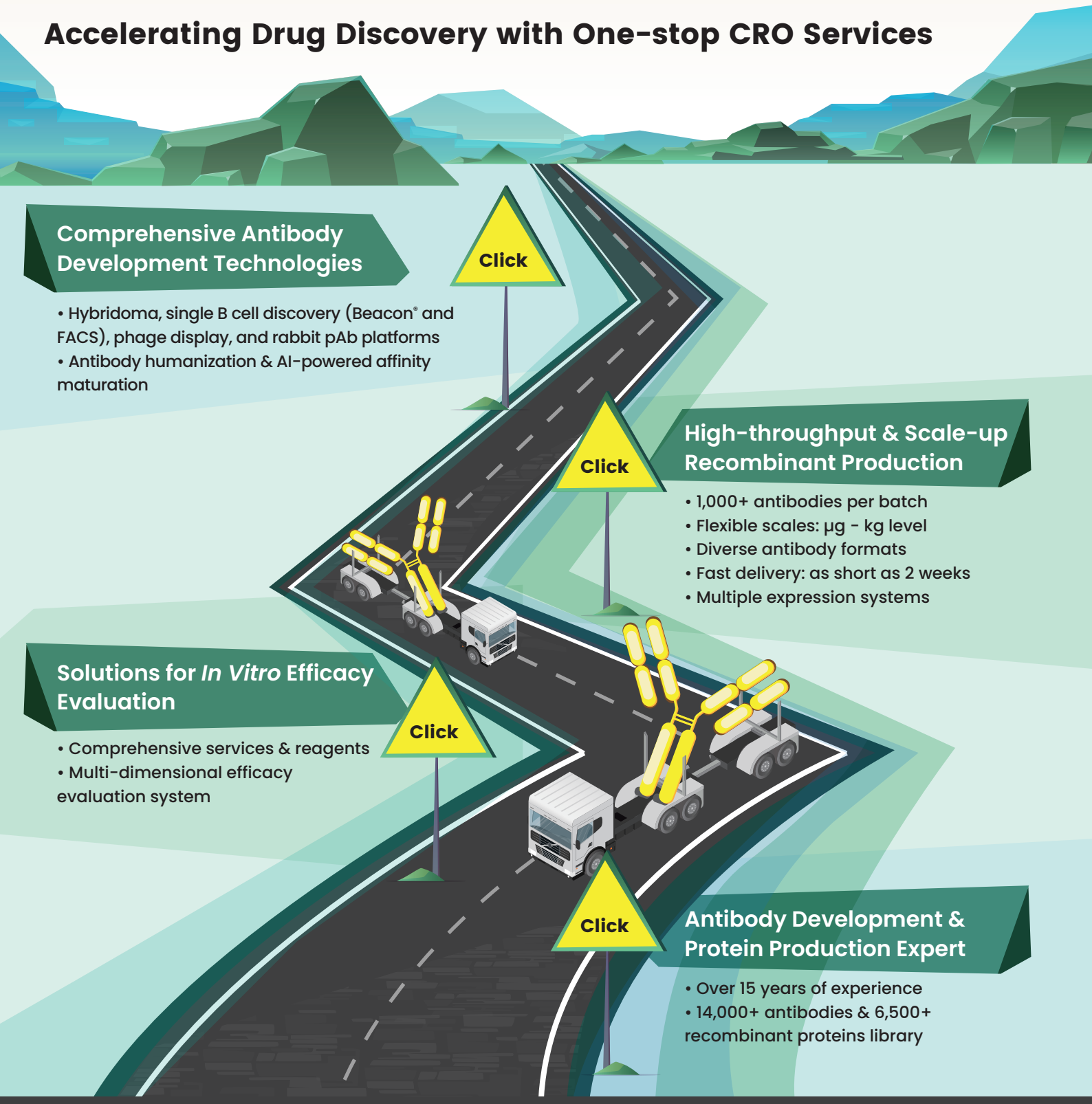

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Five years of oncology developments

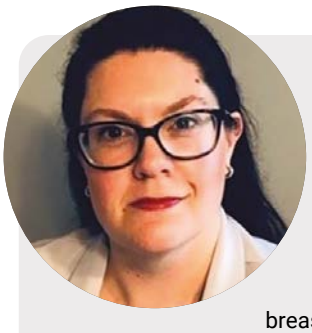
From antibody-drug conjugates and RNA, to CRISPR and CAR-T therapy, DDW's Diana Spencer asked the drug discovery industry what the most important development in oncology over the last five years has been.

Experts from across the industry were asked, "What do you feel has been the most exciting development in cancer research in the last five years?"

Dr Neil Torbett, CEO, PhoreMost: "The past five years has seen tremendous progress across many areas of cancer research; from next generation antibody-drug conjugates (ADCs), to targeted therapeutics against historically hard to drug targets.

At PhoreMost, we have been particularly excited about the emergence of targeted protein degradation (TPD) as a new therapeutic modality. The concept of harnessing the ubiquitin-proteosome system to 'destroy' or degrade disease causing proteins has been established for some time. However, over the last five years the field has rapidly advanced, in large part due to the promising clinical progression of degrader therapeutics against multiple cancer targets. This has led to an explosion of activity across pharma and biotech to progress degrader therapeutics against an array of novel targets, which may ultimately transform treatment options for both cancer and many other diseases.

Whilst first generation degrader therapeutics have predominantly harnessed a single E3 ligase to mediate protein degradation (cereblon), at PhoreMost we are focussed on unlocking other E3 ligases of which there are over 600! We are even more excited about what the next five years will bring by way of new treatment options for cancer patients."



Erin Goodhue, Director of Clinical Research and Development, and Dawn Faller, Senior Manager, Global Clinical Marketing, Therapeutic Systems, Terumo Blood and Cell Technologies: "When thinking about cancer, breast cancer has surpassed lung cancer as the most diagnosed cancer worldwide with one in eight women diagnosed in their lifetime. Triple negative breast cancer (TNBC) is the most aggressive of breast cancers, accounting for approximately 15% of all breast cancers, and is exceedingly difficult to treat. Each year there are over two million newly diagnosed breast cancer patients worldwide.

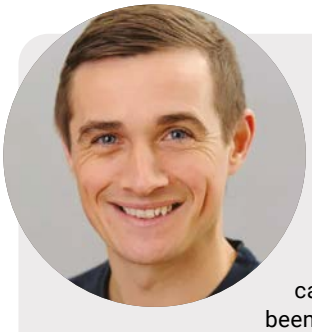
We believe one of the most exciting developments that has high potential to make a significant difference to treating cancer is the novel treatment option to TNBC patients called immunopheresis. Immunopheresis is a 'subtractive therapy,' in contrast to alternative drugs that constitute 'additive' therapies. Subtractive therapy is so exciting because it is designed to avoid the side effects, toxicity, and negative impact on a patient's quality of life that are typical of other cancer treatments. This approach combines a plasma-filtration column with a therapeutic apheresis, cell processing and cell collection platform to extract specific immune-suppressive cytokines from patient plasma that are produced by solid cancer tumours like TNBC. These targeted cytokines are selectively removed with the intention of neutralising the cancer's ability to block a patient's natural immune defence mechanisms, which are significantly compromised in late-stage, metastatic disease. This potentially re-energises the immune system to fight cancers."

> **"The past five years has seen tremendous progress across many areas of cancer research."**

Dr Jean-Nicolas Schickel, Director Cancer Immunotherapy, Vector BioPharma:

"I think that the most exciting development in oncology over the past years is the realisation that combination therapies represent the future of cancer care. Combining standard of care modalities such as chemotherapy or radiotherapy with immune checkpoints inhibitors (ICIs) has put immunotherapies firmly in the forefront of the fight against cancer. ICIs when given alone have occasionally shown poor efficacy in some indications, and in patient subpopulations with immune-excluded or immune-cold tumours. Combining multiple ICIs has shown improved efficacy, exemplified by the approval of Nivolumab plus Ipilimumab combination in MSI-high colorectal cancer in 2018. Despite this approval, the outcome for patients receiving the combination remained marginal. Very recent data from Moderna's and BioNTech's personalised vaccines in combination with ICIs in melanoma and pancreatic cancer respectively have shown dramatic improvements when given as part of a triple combination (vaccine plus ICI and chemo/radiotherapy).

I strongly believe that the next frontier to further improve patient outcomes will be to favour an immune-prone tumour microenvironment (TME). This holds the promise to broaden the application of combination therapies to non-responsive patients. However, current TME remodelling therapies such as engineered cytokines or immune cell agonists usually come with strong sides effects, which reduces therapeutic index. A precise and safe delivery system which enables local activation and/or reinvigoration of immune cells at the site of action is urgently required to finally realise the full potential of TME remodelling agents."



Billy Boyle, co-founder and CEO, Owlstone Medical:

"Some of the most exciting developments in cancer research have been the advancement of potential biomarkers within screening programmes for early detection. As well as better treatments, we are in desperate need of ways to detect cancer earlier when the chances of treatment being effective are dramatically higher. This approach is reliant on the uptake of the screening tests in the population, however, the more the invasive test, the lower the uptake.

Breath analysis be utilised is to introduce certain compounds into the body to explore how they are absorbed, metabolised, or excreted in exhaled breath – probing tumour-specific pathways and offering a readout of altered metabolism by enzymes associated with cancer. This could revolutionise screening programs to detect cancer earlier, meaning that patients can get onto relevant treatment pathways early, ultimately saving lives."

"I think that the most exciting development in oncology over the past years is the realisation that combination therapies represent the future of cancer care."

Dr Vibhor Gupta, CEO and Founder of Pangaea: "Cancer cachexia affects 40-80% of cancer patients and is attributed to 20-30% of cancer mortalities. Unfortunately, this complication remains exceedingly underdiagnosed, with up to 50% of cases being missed. This is due in part to poor screening practices and unclear clinical guidance. Early detection and intervention are essential, as cancer cachexia reduces treatment tolerance, increases treatment-related toxicity, and lowers response rates. In the UK, it is estimated that financial overhead from this complication could be as high as $1.5 billion.

Clinicians have tried to address this through manual review of patient records, but that is not a scalable solution given that it takes 40 minutes – 1 hour per patient. Technology teams have also tried addressing this using natural language processing (NLP) approaches, which look for a pre-empted set of clinical features (symptoms) based on existing medical knowledge. Given that such features can be common across several other conditions, the precision of such approaches is low and not applicable in the real world, especially given the heterogeneity of patient data.

One solution addresses these challenges by applying artificial intelligence (AI) and medical science, improving outcomes for cachectic cancer patients and reducing the burden on healthcare systems by enabling clinicians to discover six times more undiagnosed, misdiagnosed and miscoded patients who would have previously been missed through ICD-based searches or natural language processing (NLP) based approaches."

Dr Fiona McLaughlin, Chief Scientific Officer of Avacta's Therapeutics Division: "Precision oncology continues to go from strength to strength as we find new ways of tailoring therapy. The field of theranostics, a combination of diagnostics and therapeutics, has grown exponentially in the last few years. Theranostics is bringing together a specific radioactive agent which diagnoses a disease, with a second radioactive agent as treatment. This allows careful selection of specific patients that are more likely to respond to therapy, sparing patients who are less likely to respond. The PSMA targeted radiopharmaceutical Pluvicto from Novartis was the first radioligand therapy to be approved for PSMA-positive prostate cancer patients in March 2022. The protease fibroblast activation protein alpha (FAP-α) is another attractive theranostic target as it is highly expressed on cancer-associated fibroblasts and certain mesenchymal-derived tumour cells, and is expressed on up to 90% of cells in the tumour microenvironment.

FAPi PET is being developed as a highly sensitive imaging agent and can be used as a predictive biomarker for FAP targeted therapeutics, several of which are currently in clinical development. We expect this field to grow significantly in the coming years as these and other earlier stage assets are developed. The radiopharmaceutical market is expected to grow to $12 billion by 2030 and there is a substantial opportunity to grow much faster if safety and tolerability of these effective treatments can be improved."

> **"Precision oncology continues to go from strength to strength."**

Dr Michelle Fraser, Business Unit Manager, Base Editing at Revvity: "It is widely appreciated that tumours are made up of heterogeneous populations of genetically diverse cells. Oncogenic driver mutations provide immortality to dividing cells, allowing them to accumulate mutations without the consequence of programmed cell death. This understanding of tumour diversity is driving a new approach to personalised therapy. By analysing the diverse cell populations of a tumour, it is possible to predict drug responsiveness and personalise a treatment strategy to minimise the outgrowth of resistant subpopulations. The intersection of cell, protein, RNA and DNA analysis at the single cell level has advanced significantly over the last five years and is particularly informative to our understanding of cancer biology and drug responsiveness.

On the drug screening side, the rapid rise of gene modulation and knock-out using CRISPR and RNA interference is giving us unparalleled insight into the function of drug candidates. Functional genomic screens provide insight into genetic pathways, cellular processes, novel therapeutic targets, and mechanisms of action of existing or potential therapeutics. Being able to monitor the effect of a drug on a live cell population that has been specifically genetically or transcriptionally modified in proteins that the drugs may interact with gives cancer researchers and drug developers the ability to understand the function of the drug.

One of the most exciting recent developments is the use of gene editing tools to create cell and gene therapies. For example, by editing T-cells derived from a patient or a donor to have them target the cancer cells specifically, these CAR-T therapies are engaging the patient's own immune response to attack the cancer and cure the disease."

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