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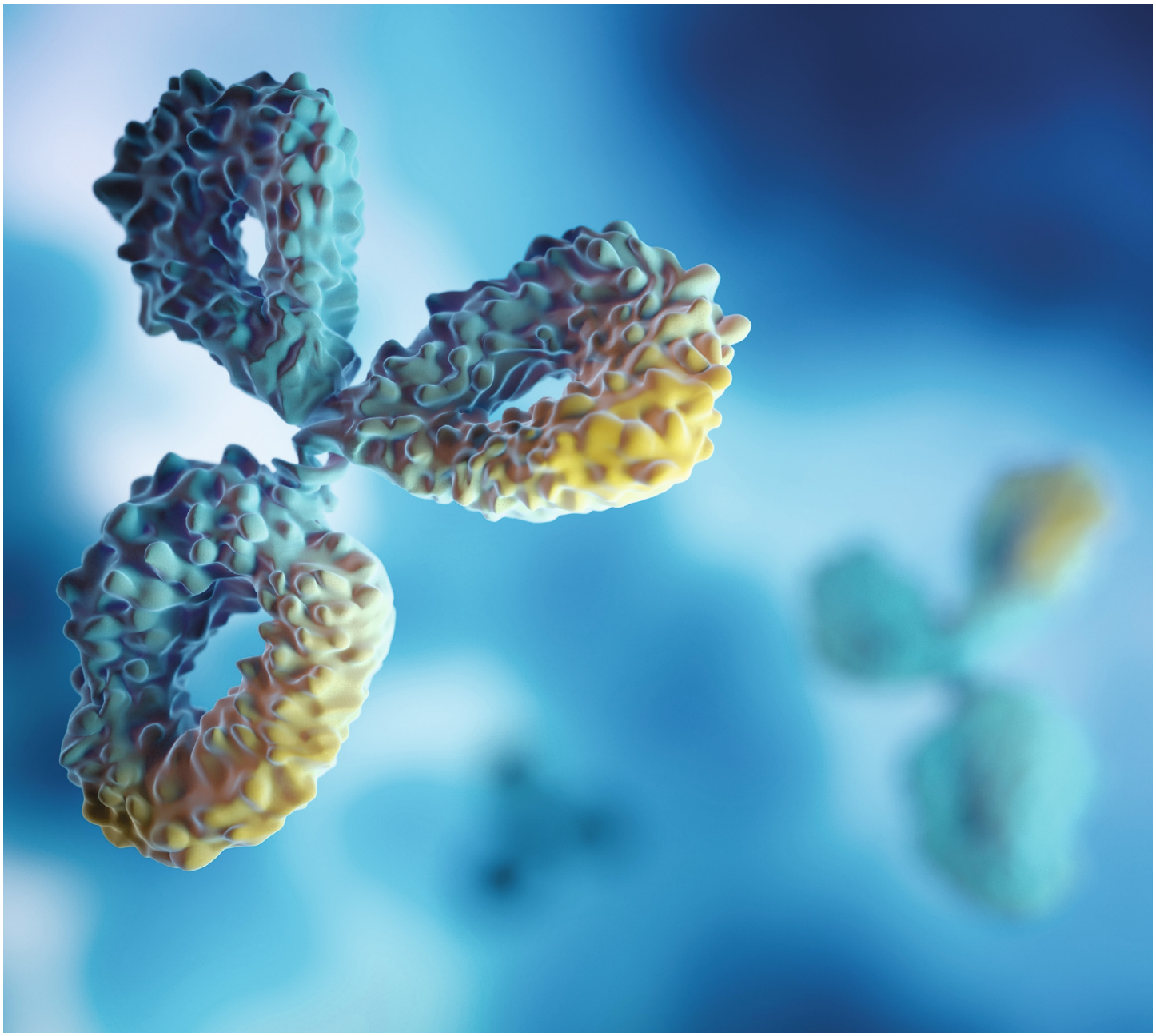

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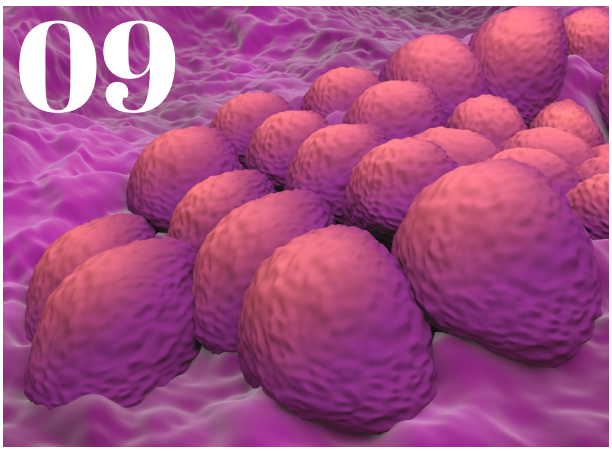

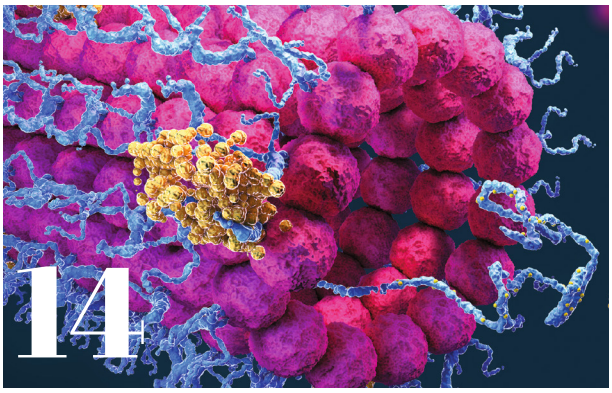

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Main office tel: + 44 (0) 203 840 4720
Website: ddw-online.com

Editor
Reece Armstrong
reece@edifydigitalmedia.com

Senior Digital Content Editor
Diana Spencer
diana@edifydigitalmedia.com

Multimedia Editor
Megan Thomas
megan@edifydigitalmedia.com

Publishing Director
Lu Rahman
lu@edifydigitalmedia.com

Sales Director
Sarah Orme
sarah@edifydigitalmedia.com

Account Director
Rich York
richard@edifydigitalmedia.com

Managing Director
Maria Wallace
maria@edifydigitalmedia.com

Production Director
Emma Bonell
emmabonell@edifydigitalmedia.com

Design
Steven Lillywhite
CRE8 Design Studios Ltd

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A therapeutic 'magic bullet'

By Diana Spencer

Since the FDA approved the first monoclonal antibody (mAb), Orthoclone, in 1986 to help prevent rejection in organ transplantation, the variety of uses for these biologics has exploded. The agency has now approved well over 100 of these so called 'magic bullets' for cancer, autoimmune and infectious diseases, and inflammatory conditions, among other indications[1]. And the scope of therapeutic mAb applications is expected to grow further in the coming years due to the development of antibody fragments, antibody derivatives and bispecific antibodies.

According to analysts Grand View Research[2], the global monoclonal antibodies market size was valued at $210.06 billion in 2022 and is projected to exhibit a compound annual growth rate (CAGR) of 11.04% from 2023 to 2030. Abbvie's Humira was the top performing mAb in 2022 with total sales of $21.24 billion, followed by Merck's Keytruda and Janssen's Stelara, with sales of $20.94 billion and $9.72 billion, respectively[3].

A range of applications

The increasing number of applications of mAb therapies as targeted treatments and rising awareness about such therapies amongst patients and physicians is expected to significantly contribute towards the market growth. The oncology segment dominated the mAbs market in 2022, accounting for 49.2% of the market value. The surge in the incidence of cancer is a key factor anticipated to drive the growth of mAbs therapeutics as they offer a precision therapy and potentially have minimal adverse effects compared to other drugs and chemotherapy interventions.

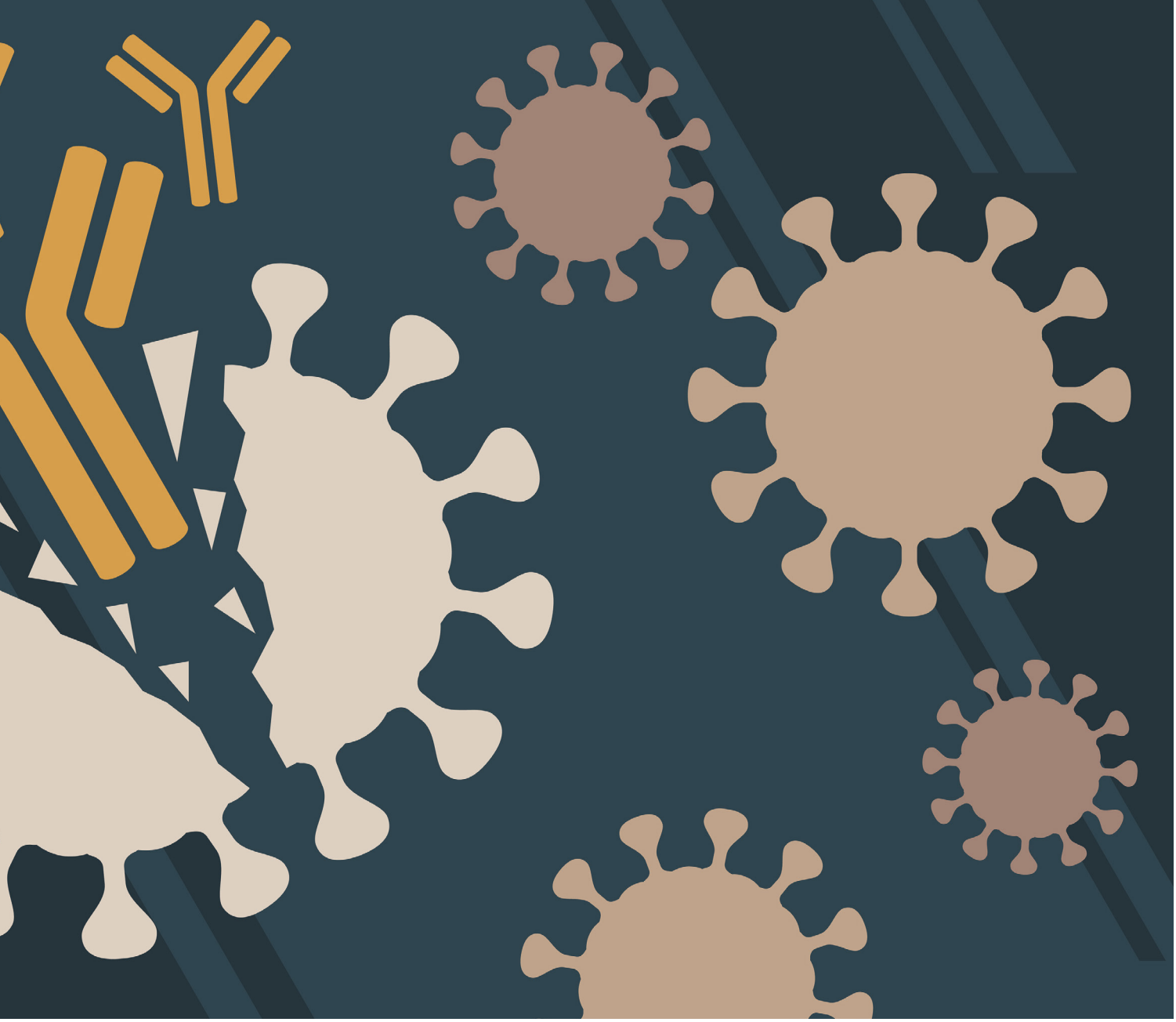
Applications of mAbs for the treatment of autoimmune diseases are also projected to grow at a lucrative rate due to the increasing prevalence of autoimmune conditions such as rheumatoid arthritis, says Grand View Research. This will also be driven by growth in the number of cytokine proteins identified in inflammatory pathways that can be targeted for disease mitigation.

In terms of region, North America recorded the largest market share of 46.1% in 2022, mainly due to increasing government expenditure for cancer research and the presence of key players such as Pfizer, Amgen and Merck, among others. The Asia Pacific region is projected to exhibit the fastest growth rate of 12.1%.

An evolving market

One significant driver for the growth of the mAb market is financial investment in the sector by the pharmaceutical industry. In one of the largest of these transactions, in early 2024, GSK acquired biotech company Aiolos Bio for a $1 billion upfront payment and up to $400 million in regulatory milestone payments. The focus of the acquisition is AIO-001, a potentially best-in-class, long-acting anti-thymic stromal lymphopoietin (TSLP) mAb, which is ready to enter Phase II clinical development for asthma, with potential for additional indications.

Monoclonal antibody developers have raised some of the largest funds in recent months. Lassen Therapeutics closed an oversubscribed $85 million Series B financing in late 2023 to fund a Phase II study in thyroid eye disease (TED) with the company's mAb LASN01 and the continued development of LASN500 for cancer. LASN01 is a first-in-class mAb targeting the receptor for IL-11 (IL-11R), while a second asset, LASN500, targets the IL-18 binding protein (IL-18BP), which is elevated at the tumour site in multiple cancer indications. Also in 2023, AbolerIS Pharma raised €27.3 million in a Series A financing to accelerate the development of its lead programme, a mAb against CD45RC, a novel molecular target expressed on a



subset of T cells that acts upstream of anti-inflammatory cytokine effectors.

In January 2024, Oxitope Pharma and Arxx Therapeutics merged to form Calluna Pharma and raised €75 million. The new company's clinical stage lead programme, CAL101, is a mAb that neutralises the bioactivity of S100A4, a DAMP protein implicated in serious and life-threatening diseases such as idiopathic pulmonary fibrosis, chronic kidney disease, systemic sclerosis, rheumatoid arthritis, and severe (steroid insensitive) asthma. Another mAb, CAL102, neutralises oxidised phospholipids, which play a significant role in onset and progression of a wide range of acute and chronic inflammatory and fibrotic diseases.

In another significant mAb collaboration, Fibrocor Therapeutics agreed a research and development (R&D) collaboration with the McQuade Center for Strategic Research and Development (MSRD) in March 2024 to advance its Alport Syndrome programme. Phase I clinical trials of mAb FIB918 are targeted to start in late 2025. William Newsome, CEO, President of Fibrocor comments: "This collaboration with the experienced team at MSRD, coupled with research funding, represents hope and potential for individuals grappling with Alport Syndrome worldwide. FIB918 has the potential to deliver a significant advancement in the treatment of patients afflicted by this debilitating disease, where current options are limited."

A promising future

The low toxicity and high specificity of monoclonal antibodies continue to make them an appealing target for clinical research and investment. However, it is this specificity that can bring limitations against evolving viral infections – several anti-SARS-CoV-2 mAbs are no longer approved for use by the FDA as they are not effective against the new dominant subvariants. Despite this, and the expense of developing mAbs, the market shows no sign of slowing down. During 2023, 16 antibody therapeutics were granted approvals in the US or EU, either for the first time or for a new indication, covering uses as diverse as cancer, Alzheimer's disease, diabetes and respiratory syncytial virus. With another 22 currently under review, it is likely we will see the potential applications for mAbs expand further in the coming years.

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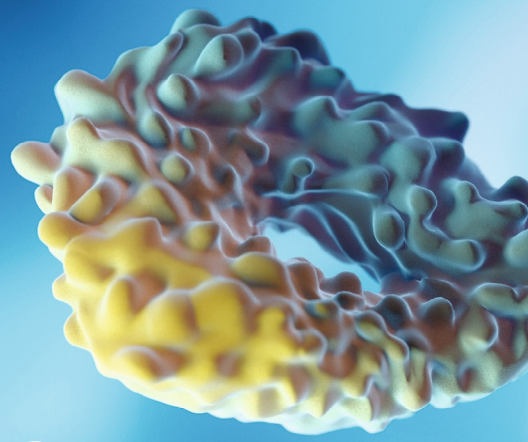
Clinical innovation in antibody therapy development



With more than 100 new antibodies entering development each year, this is a rapidly growing market with huge potential. **Diana Spencer** takes a look at the latest research into monoclonal antibodies.

There are currently 145 therapeutic antibodies approved for use around the world, with another 22 currently under review. During 2023, 16 antibody therapeutics were granted approval in the US or EU, either for the first time or for a new indication, demonstrating the vast range of uses for this type of therapeutic[1]:

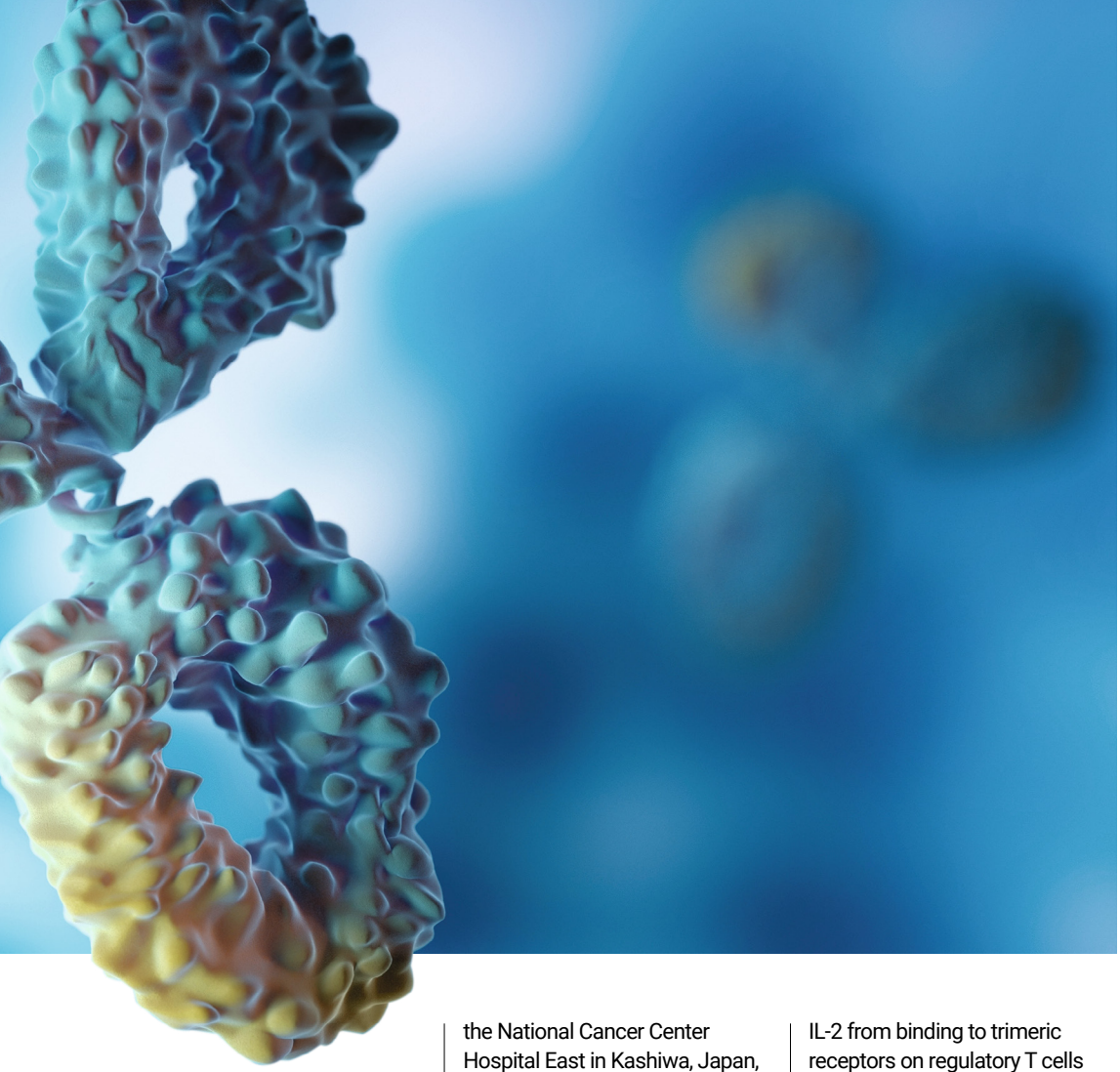
- Pozelimab (Veopoz), a complement 5; human IgG4, for CHAPLE disease
- Elranatamab (Elrexfio), a B cell maturation antigen (BCMA), CD3; humanized IgG2, for multiple myeloma
- Rozanolixizumab (Rystiggo), a FcRn; humanized IgG4, for generalised myasthenia gravis
- Talquetamab (Talvey), a G protein-coupled receptor 5D, CD3; humanized IgG4 bispecific, for multiple myeloma
- Epcoritamab (Epkinly), a CD20, CD3; bispecific humanized IgG1, for diffuse large B cell lymphoma
- Lebrikizumab (Ebglys), an IL-13; humanized IgG4, for atopic dermatitis
- Glofitamab (Columvi), aCD20, CD3e; bispecific 2+1 IgG1 CrossMab, for diffuse large B-cell lymphoma
- Mirikizumab (Omvoh), an IL-23p19; humanized IgG4, for ulcerative colitis
- Tislelizumab (Tevimbra), a PD-1; humanized IgG4, for esophageal squamous cell carcinoma
- Toripalimab (Loqtorzi, Tuoyi), a PD-1; humanized IgG4, for nasopharyneal carcinoma, esophageal squamous cell carcinoma
- Retifanlimab (Zynyz), a PD-1; humanized IgG4, for Merkel cell carcinoma
- Lecanemab (Leqembi), an amyloid beta protofibrils; humanized IgG1, for Alzheimer's disease
- Teplizumab (Tzield), a CD3; humanized IgG1, to delay onset of type 1 diabetes
- Ublituximab (Briumvi), a CD20; chimeric IgG1, for multiple sclerosis
- Mirvetuximab soravtansine (Elahere), a folate receptor alpha; humanized IgG1 antibody-drug conjugate (ADC), for ovarian cancer
- Nirsevimab (Beyfortus), RSV; human IgG1, for respiratory syncytial virus (RSV) infection

> **Monoclonal antibody infusion could offer protection against HIV acquisition.**

Oncology applications

The regulatory achievement is even greater, when it is considered that these molecules only have approval success rates of 14-32%, with higher rates for non-cancer indications[2]. This low percentage indicates that monoclonal antibodies to treat cancer are challenging to develop and gain regulatory acceptance for, and yet this is one of the most exciting disease areas for antibodies. More than 100 new experimental antibodies enter into development each year, and despite the likely hurdles, half of these are potential cancer therapeutics[3].

To support their development, the US Food and Drug Administration (FDA) granted Fast Track Designation to several antibody treatments in 2023, a status created to expedite the review of new medicines that intend to treat serious or life-threatening conditions with



unmet medical needs. These included Alentis Therapeutics' investigational monoclonal antibody ALE.C04 for recurrent or metastatic CLDN1-positive head and neck squamous cell carcinoma (HNSCC). ALE.C04 is designed to treat cancer by remodelling the extracellular matrix, leading to improved natural killer (NK) and T cell trafficking, and direct tumour cell killing through the effector function. The company is investigating the mAb in a Phase I/II clinical trial as both a monotherapy and in combination with pembrolizumab.

In another example of mAbs' value in treating cancers with previously poor outcomes, in March 2024, Japan was the first country to approve Astellas's Vyloy (zolbetuximab), an anti-claudin 18.2 (CLDN18.2) monoclonal antibody for patients with CLDN18.2 positive, unresectable, advanced or recurrent gastric cancer. Kohei Shitara, Head, Department of Gastrointestinal Oncology, the National Cancer Center Hospital East in Kashiwa, Japan, comments: "Developing new targeted therapies is critical for diseases like advanced gastric adenocarcinoma, which has had very limited treatment options and is often discovered at an advanced stage. As the primary investigator for the Phase III SPOTLIGHT clinical trial, I witnessed firsthand the significant improvement in progression-free survival and overall survival for patients treated with Vyloy in combination with chemotherapy compared to those treated with placebo plus chemotherapy."

Innovative technologies are opening up new potential treatment avenues for mAbs in cancer. AU-007 from Aulos Bioscience is currently being investigated in a Phase I/II clinical trial and represents a novel approach to solid tumours. The computationally designed, human IgG1 monoclonal antibody is highly selective to the CD25-binding portion of IL-2 and leverages IL-2 to reinforce anti-tumour immune effects. This is achieved by preventing IL-2 from binding to trimeric receptors on regulatory T cells while still allowing IL-2 to bind and expand effector T cells and NK cells. The company hopes this will prevent the negative feedback loop caused by other IL-2-based treatments and biases the immune system toward activation over suppression.

mAbs beyond cancer

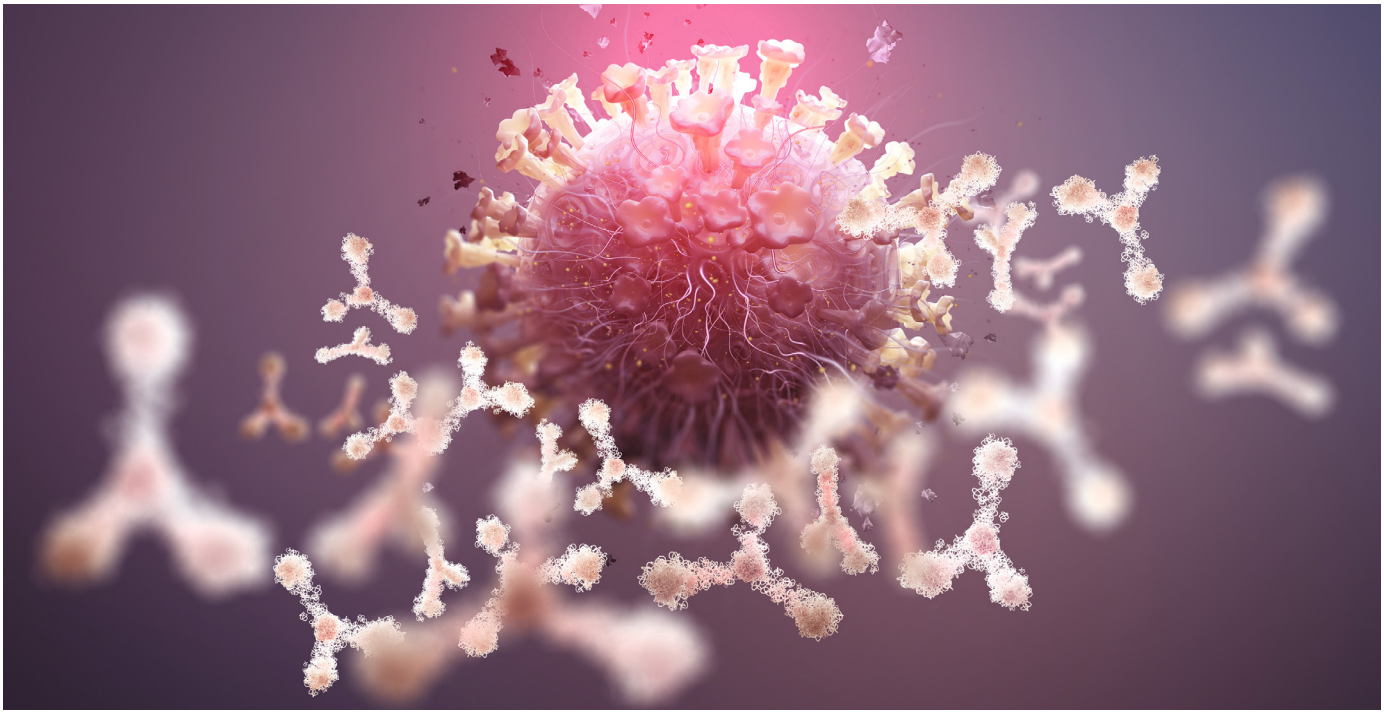
mAbs have a variety of applications outside oncology. One indication of promise for mAbs is in neurodegenerative diseases. In 2023, Eisai and Biogen's Leqembi (lecanemab) became the second anti-amyloid beta (Aβ) mAb to be approved by the FDA for the treatment of Alzheimer's disease (AD), following the approval of Biogen's Aduhelm (aducanumab) in 2021. The mAb demonstrated both a reduction in Aβ and a 27% reduction in clinical decline in its Phase III Clarity AD trial.

> **These molecules only have approval success rates of 14-32%, with higher rates for non-cancer indications.**

ImmunoBrain Checkpoint (IBC) is also pursuing mAbs for AD and is currently dosing patients in a Phase I clinical trial to evaluate its lead asset, IBC- Ab002. Professor Michal Schwartz tells DDW: "Our approach is to leverage the power of the immune system to help clear the toxic proteins as well as to arrest the local brain inflammation through endogenous mechanisms. By rejuvenating the immune system, a natural process within the body, our approach seeks to restore overall ability of the brain to fight the disease instead of directly targeting specific hallmarks of the pathology."

Autoimmune diseases are another key target area for mAbs. Biotechnology company ImmunAbs recently reported a successful Phase I clinical trial for IM-101, a humanized mAb targeting complement C5, which is widely acknowledged for its critical involvement in autoimmune diseases. IM-101 demonstrated good tolerability, with no severe adverse events or dose limiting toxicity, and met all predefined endpoints. The company plans to progress to Phase II trials.

mAbs have also demonstrated efficacy in treating the dermatological condition hidradenitis suppurativa (HS). UCB demonstrated a 55% improvement in adults with moderate to severe HS treated with mAb bimekizumab. Bimekizumab treatment demonstrated improvements in overall lesion count and lesion clearance, across abscesses, inflammatory nodules and draining tunnels over 48 weeks. In addition, patient-reported data showed that high levels



of clinical responses observed with bimekizumab treatment translated into benefits in health-related quality of life.

Viral infections

mAbs have gained regulatory approval and continue to be investigated as potential therapeutics and prophylactics for a number of viral infections, due to their high specificity and ability to enhance immune responses. In 2023, the FDA approved AstraZeneca's Beyfortus (nirsevimab-alip) for the prevention of respiratory syncytial virus (RSV) in neonates and infants and in children up to 24 months of age who remain vulnerable to severe RSV.

In March 2024, the FDA granted emergency use authorisation (EUA) to half-life extended monoclonal antibody (mAb) Pemgarda (pemivibart, or VYD222) for the pre-exposure prophylaxis of Covid-19 in patients who are moderate-to-severely immune compromised. Several other anti-SARS-CoV-2 mAbs (bamlanivimab plus etesevimab, casirivimab plus imdevimab, sotrovimab, and bebtelovimab) have received EUAs from the FDA in past years for the treatment of outpatients with mild to moderate Covid-19. However, these mAbs are not currently authorised for use because the dominant Omicron subvariants are not expected to be susceptible to these products.

> **By rejuvenating the immune system, our approach seeks to restore overall ability of the brain to fight the disease.**

mAbs have shown some potential as prevention and treatment for HIV. A study in *The Journal of The International AIDS Society* analysed broadly neutralising monoclonal antibodies for HIV prevention[4]. The authors write: "Recently, two antibody-mediated prevention (AMP) trials of a passively administered monoclonal antibody targeting the HIV envelope CD4 binding site, called VRC01, provided proof-of-concept that monoclonal antibody infusion could offer protection against HIV acquisition. While the trials failed to show overall protection against HIV acquisition, sub-analyses revealed that VRC01 infusion provided a 75% prevention efficacy against HIV strains that were susceptible to the antibody."

In a 2022 study published in JAMA, the author found that treatment with two mAbs completely suppressed HIV for about 40 weeks in patients who participated in a small Phase I trial[5]. Meanwhile, another 2022 study demonstrated that combination therapy with broadly neutralising mAbs can provide long-term virological suppression without antiretroviral therapy in individuals with HIV[6].

More recently, Theratechnologies evaluated an intramuscular (IM) method of administration for Trogarzo (ibalizumab-uiyk), a mAb antiretroviral therapy (ART) for the treatment of heavily treatment-experienced adults with multidrug-resistant (MDR) HIV-1 infection failing their current antiretroviral regimen. Although the primary endpoint measuring a 90% confidence interval of the ratio of IM injection to IV infusion did not meet the equivalence limits, viral suppression, a key secondary clinical endpoint, was maintained in all HIV-positive subjects throughout the study.

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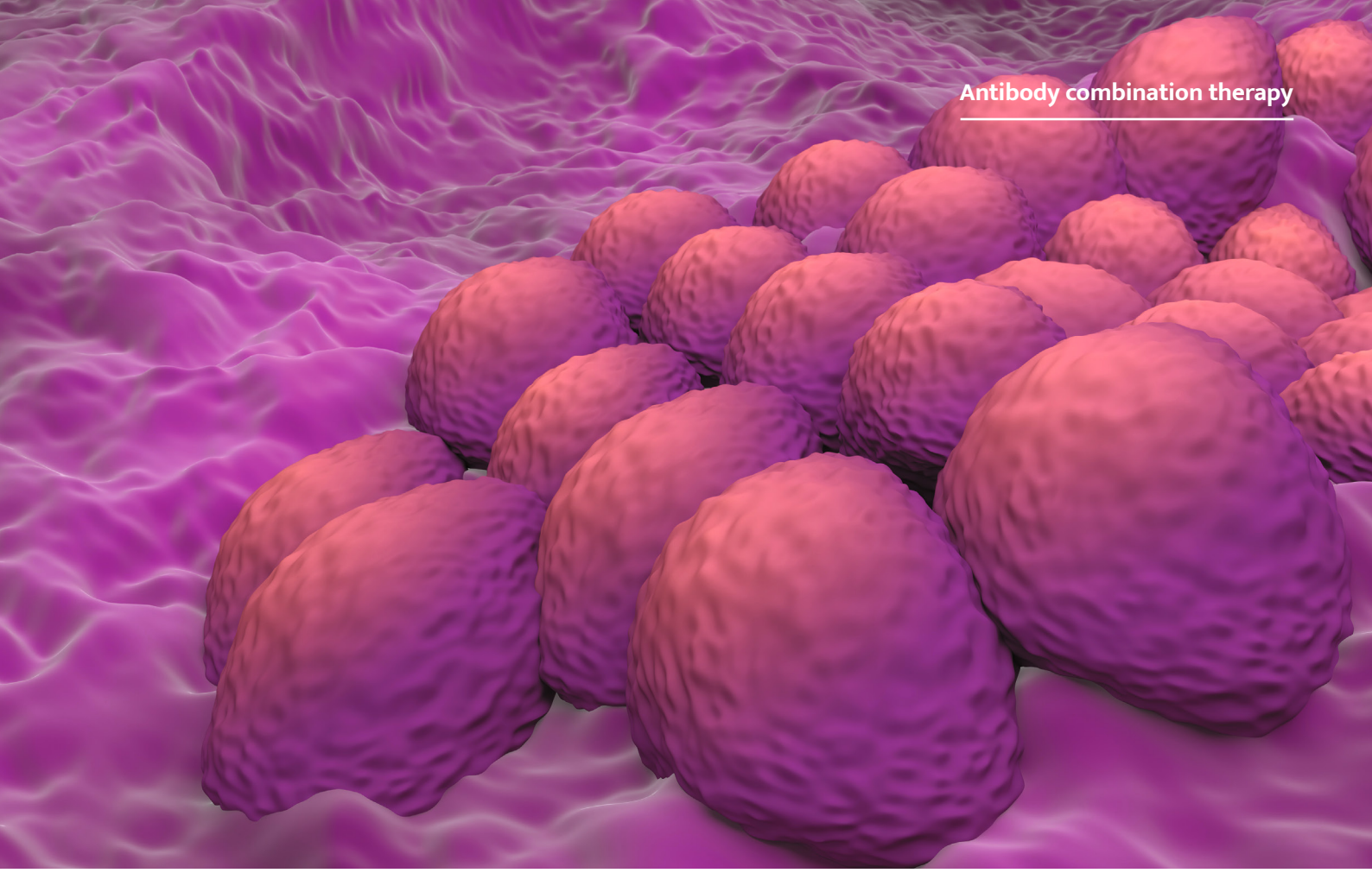

Improving the standard of care: Inside the DUO-E trial

Professor Shannon Westin is principal investigator of the DUO-E trial. Here she speaks to DDW's **Megan Thomas** about why the standard of care needs improving and the impact of therapeutic antibodies such as durvalumab.

The DUO-E trial is a three-arm, randomised, double-blind, placebo-controlled, multicentre Phase III trial assessing the combination of durvalumab with platinum-based chemotherapy followed by durvalumab with or without olaparib maintenance therapy as a treatment for patients with newly diagnosed advanced or recurrent endometrial cancer. In the DUO-E trial, patients were randomised 1:1:1 to Control arm – platinum-based chemotherapy and durvalumab placebo followed by durvalumab placebo and olaparib placebo; durvalumab arm – platinum-based chemotherapy and durvalumab followed by durvalumab and olaparib placebo; and durvalumab plus olaparib arm – platinum-based chemotherapy and durvalumab followed by durvalumab and olaparib. The dual primary endpoint was progression free survival (PFS) comparing durvalumab plus olaparib arm vs Control arm and durvalumab arm vs Control arm.

> **These data offer clinical community evidence for novel avenues to provide incremental benefit for endometrial cancer patients.**

Dr Shannon Westin says: "I am very excited about the DUO-E trial results as they showed that durvalumab plus platinum-based chemotherapy, followed by either durvalumab monotherapy or durvalumab plus olaparib, both demonstrated a statistically significant and clinically meaningful improvement in progression-free survival compared to chemotherapy alone in the overall trial population of patients with newly diagnosed advanced or recurrent endometrial cancer."

Dr Westin explains that the results showed that treatment with durvalumab plus chemotherapy followed by durvalumab plus olaparib (durvalumab plus olaparib arm) and treatment with durvalumab plus chemotherapy followed by durvalumab monotherapy (durvalumab arm) demonstrated a reduction in the risk of disease progression or death, by 45% (hazard ratio [HR] 0.55; 95% confidence interval [CI] 0.43-0.69; p<0.0001) and 29% (HR 0.71; 95% CI 0.57-0.89; p=0.003), respectively, versus chemotherapy alone (Control Arm). Median PFS was 15.1 months in the durvalumab plus olaparib arm. Interim overall survival (OS) data showed a favourable trend for both treatment regimens versus control in the overall population. Therefore, DUO-E confirms the clinical benefit of adding immunotherapy to chemotherapy in the treatment of advanced or recurrent endometrial cancer and is the first Phase III study to demonstrate that the addition of olaparib confers benefit in this setting.

In addition, in a prespecified exploratory analysis by mismatch repair status, similar results were achieved with both treatment arms in dMMR patients: 59% (HR 0.41; 95% CI 0.21-0.75) and 58% (HR 0.42; 95% CI 0.22-0.80) for the durvalumab plus olaparib arm and durvalumab-only arm, respectively, compared with chemotherapy alone. However, in patients with mismatch repair proficient disease (pMMR) the durvalumab-only arm saw a reduction in the risk of progression or death of 23% (HR 0.77; 95% CI 0.60-0.97), which was increased to 43% (HR 0.57; 95% CI 0.44-0.73) when olaparib was added to durvalumab and median PFS was 15 months in the durvalumab plus olaparib arm versus 9.7 months in the Control arm.

> **In recent years we have seen the successful emergence of antibody combination therapy approaches across a variety of tumour types.**

"These DUO-E data offer clinical community evidence for novel avenues to provide incremental benefit for endometrial cancer patients," Dr Westin adds.

Standard of care

According to Dr Westin, endometrial cancer is the sixth most common cancer in women worldwide and the only cancer where incidence and mortality continue to rise driven in part by an ageing population and the obesity epidemic. This, she says, is why the standard of care requires improvement and why new treatment options that can better serve a wide range of patients are needed, particularly at advanced stages. She says: "Most patients with endometrial cancer are diagnosed at an early stage and the five-year survival rate is high in this setting (approximately 95%). However, for patients with advanced disease (stage III-IV), prognosis remains poor, with a five-year survival rate of approximately 20-30%."

dMMR and pMMR patient results

On the topic of how important it is that the study saw results in both mismatch repair deficient (dMMR) and mismatch repair proficient (pMMR) patients, Dr Westin says: "Currently, the global standard-of-care treatment for advanced or recurrent endometrial cancer

is hormonal therapy or platinum-based combination chemotherapy, specifically carboplatin and paclitaxel. Recently, we have seen immunotherapy combined with chemotherapy emerging as a new standard of care, particularly for patients with mismatch repair deficient (dMMR) disease. But there remains a high unmet need for new treatment options for patients with mismatch repair proficient (pMMR) disease, who comprise approximately 80% of patients with endometrial cancer."

She continues to say that what this is why the results of DUO-E are so interesting, as they build on these recent advancements with immunotherapies by adding a PARP inhibitor to the combination and are important as there is a high unmet need for new treatment options for patients with pMMR endometrial cancer.

She adds: "As I mentioned in a prespecified exploratory analysis by mismatch repair status, similar results were achieved with both treatment arms in dMMR patients: 59% (HR 0.41; 95% CI 0.21-0.75) and 58% (HR 0.42; 95% CI 0.22-0.80) for the durvalumab plus olaparib arm and durvalumab-only arm, respectively, compared with chemotherapy alone. However, in patients with mismatch repair proficient disease (pMMR) the durvalumab-only arm saw a reduction in the risk of progression or death of 23% (HR 0.77; 95% CI 0.60-0.97), which was increased to 43% (HR 0.57; Therapeutic antibodies: DUO-E trial 95% CI 0.44-0.73) when olaparib was added to durvalumab and median PFS was 15 months in the durvalumab plus olaparib arm versus 9.7 months in the Control arm."

PD-L1 for tumours

PD-L1 has become an important biomarker for tumours responding to immunotherapies but this study still saw some benefit in PD-L1 negative patients. When asked if this is due to the combination approach of both the immunotherapy and PARP inhibitor, Dr Westin says: "Durvalumab enhances the anti-tumour immune response by overcoming PD-L1-mediated inhibition of T cells. Chemotherapy complements durvalumab through its potential to enhance immune priming and through direct tumour cell killing. Olaparib leads to the accumulation of DNA damage in tumour cells through the inhibition of PARP, which can lead to tumour cell death. In addition, inhibition of PARP can also have immunomodulatory effects that work together with durvalumab to further enhance the anti-tumour immune response.

> **There remains a high unmet need for new treatment options for patients with mismatch repair proficient (pMMR) disease.**

"PD-L1 is a known biomarker for durvalumab in other indications and a prespecified analysis based on PD-L1 status showed that in the PD-L1 positive population (tumour area positivity score [TAP] ≥1%), treatment in the durvalumab and the durvalumab plus olaparib arms reduced the risk of disease progression or death by 37% (HR 0.63; 95% CI 0.48-0.83) and 58% (HR 0.42; 95% CI 0.31-0.57), respectively, versus the Control arm. Median PFS was 20.8 months in the durvalumab plus olaparib arm versus 9.5 months in the Control arm. In the PD-L1 negative population (TAP<1%), treatment in the durvalumab and the durvalumab plus olaparib arms reduced the risk of disease progression or death by 11% (HR 0.89; 95% CI 0.59-1.34) and 20% (HR 0.80; 95% CI 0.55-1.16) respectively, versus the Control arm."

Opportunities and challenges

Dr Westin says that this study is indicative of other successful therapeutic antibody combination therapy approaches we've seen in cancer, highlighting that in recent years we have seen the successful emergence of antibody combination therapy approaches across a variety of tumour types. She notes: "What is different about DUO-E is by building on this foundation we are also bringing in PARP inhibition, expanding the effect to patients who wouldn't normally see as great a benefit with the addition of immunotherapy alone. I'm looking forward to seeing additional DUO-E trial results which will be presented at upcoming medical meetings."

Dr Westin says that resistance to therapy remains a critical challenge and one of the biggest unmet needs for these patients. She says: "To understand mechanisms of resistance, we build in translational endpoints including assessment of liquid and tissue biospecimens. This allows us to develop future trials and treatments that will prevent or overcome this resistance."

Originally published in DDW Volume 25 – Issue 1, Winter 2023/2024 – Therapeutic Antibodies Guide

Biography:

Professor Shannon Westin is the Professor of Gynecologic Oncology and Reproductive Medicine in the Division of Surgery at The University of Texas MD Anderson Cancer Center, and principal investigator of the DUO-E trial.

Understanding residual DNA testing in biopharmaceutical production

Within the field of monoclonal antibody therapies, the significance of robust product characterisation cannot be overstated. It is a key component of many quality assurance and quality control parameters, as well as necessary for regulatory compliance. One of the key aspects of this process is the quantitation of residual DNA within a bioproduction workflow. Ensuring the safety, efficacy, purity, quality, and potency of the final drug product is contingent on meeting strict regulatory guidelines.

What is residual DNA?

Residual DNA remains from the host cells used in biotherapeutics production. It is considered an impurity, and its quantitation is a critical component of the product characterisation process. The amount of residual DNA contained in the final drug product must meet specific regulatory guidelines to ensure patient safety.

The development of residual DNA assays comes with its own set of challenges; it requires expertise, resources, and time. Typically, these assays are developed, validated, and used as a quantitative test for impurities. This involves the development of multiple documents, including standard operating procedures (SOPs) for the test method, critical reagent preparation and qualification, equipment operation and maintenance, method development report, and validation protocols and reports.

Given the complexities of the process, a key consideration for manufacturers is whether to develop an in-house assay or opt for a commercial kit. There are several factors to consider in this decision. First, does the organisation have the necessary expertise and internal development capabilities? Secondly, while commercial kits might appear costly upfront, there are hidden costs associated with developing an in-house assay, including the resources and time required for development, implementation, and troubleshooting.

The technologies and your workflow

Part of the necessary expertise lies in offering solutions that leverage the latest techniques that can be applied to various workflows. Within quantitating residual DNA, two powerful technologies have emerged as key players: quantitative PCR (qPCR) and digital PCR (dPCR).

qPCR is a well-established method used for residual DNA quantitation. It uses real-time measurements, relying on a standard curve for relative quantitative data. This technology is widely utilised due to its broad dynamic range and high-throughput capability. Furthermore, it can rapidly amplify and quantify target DNA sequences, providing real-time data that is both precise and reliable.

dPCR, on the other hand, is a newer technology that also holds great promise in the field. Unlike qPCR, dPCR achieves absolute quantification of known genetic targets without the need for a standard curve. This enhances the precision and reproducibility compared to other quantitative methods. This makes dPCR an invaluable tool for accurate and reliable quantification in genetic analysis.

Both qPCR and dPCR are complementary technologies, and the choice between them depends on workflow preferences and application-specific requirements.

Designed in-house vs commercial solutions

Developing an in-house assay requires significant internal resources, such as time, money, and in-house capabilities. It further entails identifying and validating component sources and managing multiple suppliers. On the other hand, commercially available kits can provide tested, standardised, and optimised components, saving both time and money and mitigating potential risks during biologic manufacturing.

These kits eliminate the need for time-consuming and resource-intensive in-house method development and can be validated. The Applied Biosystems resDNASEQ Residual DNA Quantitation

Kits have been developed to help enable residual DNA testing to meet or exceed the most rigorous regulatory guidelines. The streamlined workflow typically includes instrumentation and analytical software, helping to significantly reduce assay development and optimisation time.

Commercially available kits, from established suppliers, adhere to rigorous standardisation processes that have been validated for accuracy and consistency. Furthermore, they have been optimised to deliver exceptional sensitivity and specificity. These quality control processes minimise the risks of contamination, variability, and other factors that can negatively impact results. This is especially crucial when transitioning beyond preclinical drug development into method development strategies. Furthermore, commercially available kits help enable the user to gain access to the developer's expertise. The support often includes instrument installation assistance, user training, assay setup, troubleshooting, and even some data interpretation. Technical support proves invaluable for researchers new to a particular assay or technique.

The overall workflow – and specifically the resDNASEQ Residual DNA Quantitation kit – is scalable, accommodating experiments of varying sizes and easily adaptable to changing needs, including specific manufacturing processes and product types. This scalability can be especially helpful to facilitate data accuracy for in-process or lot-release samples.

Arguably the most compelling reason to opt for a commercially available kit over an in-house developed assay (so-called "homebrewed assay") is convenience. Manufactured kits are designed to provide the necessary components to complete a project in a simple and easy-to-follow format. Overall, commercially available kits for residual DNA testing offer numerous advantages, including enhanced sensitivity, time and cost efficiency, improved product consistency, regulatory compliance, and access to expert technical support. Leveraging these kits can help streamline the biologic manufacturing workflow in terms of processes, strong quality control, and enable the safety and efficacy of the final product.

The resDNASEQ system is a fully integrated assay leveraging real-time PCR technology for quantitation of residual host cell DNA with a qualified DNA reference standard. The assay, which can be run on the Applied Biosystems QuantStudio 5 Real-Time PCR System or the Applied Biosystems 7500 Fast Real-Time PCR Systems, features complete residual host cell or plasmid DNA testing workflows from sample preparation to results in less than five hours. The system has been widely adopted for routine in-process and lot release use at major biopharma companies worldwide. Additionally, there are several resDNASEQ Quantitation Kits that are now available as dPCR kits to be used on the Applied Biosystems QuantStudio Absolute Q Digital PCR System.

Residual DNA testing is a critical aspect of biopharmaceutical production. Both qPCR and dPCR offer robust solutions to help provide accurate data. Their complementary strengths provide manufacturers with versatile tools to meet stringent regulatory standards and deliver high-quality productions. Furthermore, whether opting for an in-house developed assay or a commercial solution, it's essential to consider the expertise, cost, and time implications. Whether you decide to use a qPCR or dPCR solution, the Applied Biosystems SEQ portfolio can meet your needs. Learn more about our residual host cell DNA quantitation solutions today.

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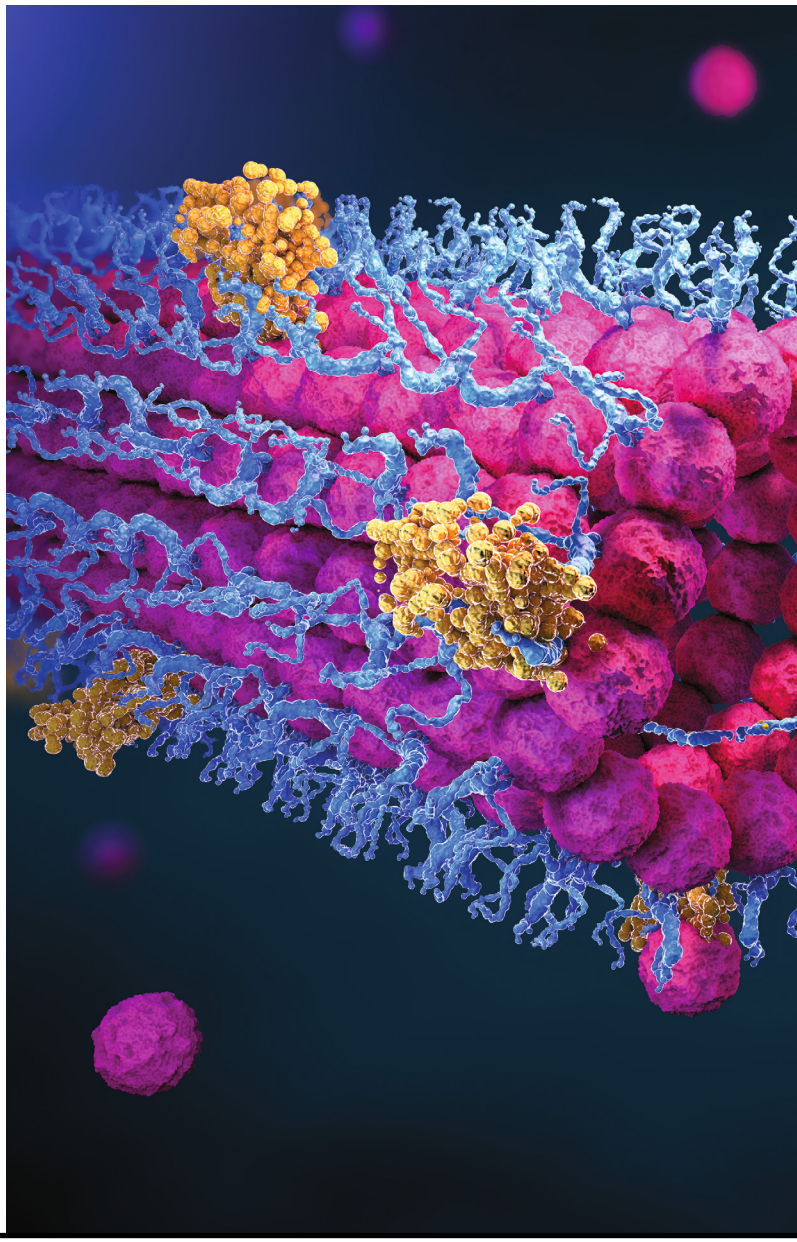
The latest advances in protein and antibody engineering

DDW's **Megan Thomas** attended PEGS Europe 2023 in Lisbon, Portugal. Here, she shares insight from the annual biologics technology meeting.



Scientific tracks and presentations

Antibody-based cancer therapies

The first presentation attended in the antibody-based cancer therapies track, within the antibody drug conjugate (ADC) session, was called: 'A new era of single-cell functional profiling for drug discovery', presented by Kathrin Herbst, PhD, Director of Science & Business Development at Lightcast. Lightcast is developing a novel, programmable microfluidic platform that allows precise and highly flexible control of individual microdroplets using software-generated light patterns. The company's goal is to accelerate functional characterisation and shorten optimisation time in antibody discovery and T cell workflows. In addition, live cells of interest can be rapidly dispensed for downstream assays as droplets remain individually addressable throughout.

Cell line and systems engineering

Following this, a presentation in the cell line and systems engineering track, focused on applying data science to enhance protein expression, 'Using machine learning to predict protein expression', was presented by Lovisa Holmberg Schiavone, PhD, Director, Discovery Biology, Discovery Sciences, R&D, AstraZeneca – though Holmberg Schiavone made note of the various contributors and collaborators in the poster which was being presented, including protein scientist in machine learning, Evgeny Tankhilevich. This presentation covered three primary drivers for a protein expression model: speed, cost and sustainability. "It has been a learning journey for us," Holmberg Schiavone shared, and emphasised the importance of data sharing as a model of the future.

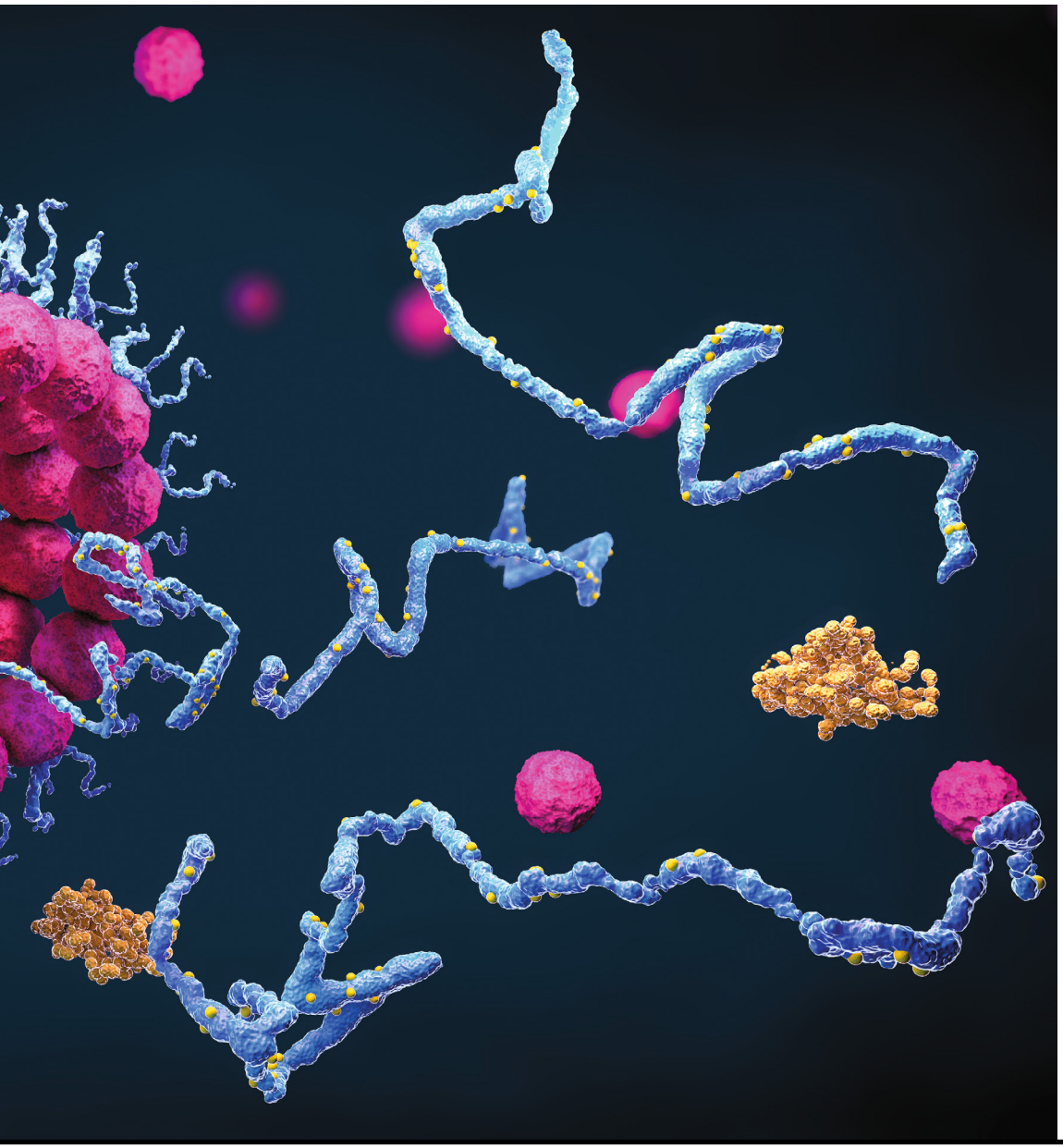
The next presentation attended in this track was the keynote presentation, which was given by Kate Smith, PhD, Head of UK Protein & Cell Sciences at GSK. GSK has developed high-throughput mammalian and E. coli expression systems and is using high-throughput expression pipelines to screen constructs for optimal expression to generate protein and cellular reagents. The presentation introduced the company's high-throughput expression systems, its approaches to organising data and its design approaches.

Optimisation and developability

The final presentation attended on the first day of PEGS Europe 2023 was in the track on optimisation and developability, within the immunogenicity risk assessment session, titled: 'Accelerating antibody discovery for difficult targets through mRNA immunisation and beacon single cell technology'. It was presented by Francois Romagne, PhD, Scientific Director of MI-mAbs. The presentation engaged with how classical immunisation strategies and subsequent hybridoma generation often face strong limitations when it comes to poorly immunogenic membrane proteins with short extracellular domains – even though there is demonstrated efficiency in antibody generation. As such, Romagne shared how the obtention of large collections of antibodies with both molecular and function diversity against a difficult GPCR and ion channel will be described using innovative approaches combining RNA immunisation and single cell screening.

Emerging targets and therapeutic approaches

The first attended session in the emerging targets and therapeutic approaches track was the keynote within the session on innovative approaches to the challenges of solid tumours. It was presented by Xiaole Shirley Liu, PhD, CEO, GV20 Therapeutics, and titled: 'AI-based target and antibody discovery from patient tumour profiles'. She presented on how GV20 uses bioinformatics and AI to decode natural B-cell responses from large cohorts of patient tumours to uncover novel targets and antibodies simultaneously and has brought a first-in-class antibody against a novel innate checkpoint to Ph1 clinical trial in the US.



Advancing bispecifics and combination therapy to the clinic

Next was a presentation on novel approaches. It was by Nicholas Field, Principal Scientist, Purification Development, Lonza, titled: 'Tailored CMC solutions to overcome the challenges in bispecific, Fab and Fc-fusion protein development programs'. Lonza's integrated CMC strategy and timeline was presented, as well as case studies highlighting key approaches and technologies, including: vector design & integration, cell line selection, downstream process, analytical method and formulation development. Field also covered the capabilities and strategies that enable acceleration of Fc-fusion, Fab fragment and bispecific antibodies through pre-clinical development.

This was followed by another presentation on harnessing neutrophils using bispecifics. It was presented by Lei Shi, PhD, Senior Vice President, R&D, Biointron Biological, titled: 'Accelerating early discovery through HTP and high-speed antibody production'. Shi talked about Biointron's high-efficiency expression platform that enables two-week antibody production services, and how the company's FC-MES affinity maturation system is able to provide non-

biased antibody optimisation and affinity maturation in less than two months.

CAR-T cell therapies and *in vivo* solutions

Chad May, CSO of Serotiny, presented on: 'Improving cell therapies with high-throughput CAR libraries', in the session relating to optimising CARs. He shared how Serotiny has demonstrated the use of its high-throughput platform to build and deliver CARs that improve *in vivo* responses in preclinical studies.

Finally, a panel discussion asked: 'What is the next game changer in the CAR T cell field?' Panel moderators included Ulf Grawunder from T-CURX and Astero Klampatsa from the Institute of Cancer Research, and panellists included John Anderson from University College London, Michael Hudecek from University of Applied Sciences Wuerzburg-Schweinfurt, as well as Sebastian Kobold from Klinikum de Universität München. Despite the weighty topic and a limited time frame, they engaged in depth on the various ways the CAR T cell field will expand in the future, and where its success lies in the present.

Protein process development

In the protein purification session, Anis Larbi, Senior Manager Medical & Scientific Affairs, Beckman Coulter Life Sciences, presented on reducing the complexity of protein manufacturing and streamlining the workflow. In the presentation, he discussed how technological platforms integrated to a workflow improve reproducibility and robustness of the process, highlighting the various steps of protein manufacturing from inception of the idea to the final quality control of the end-product.

Next-generation immunotherapies

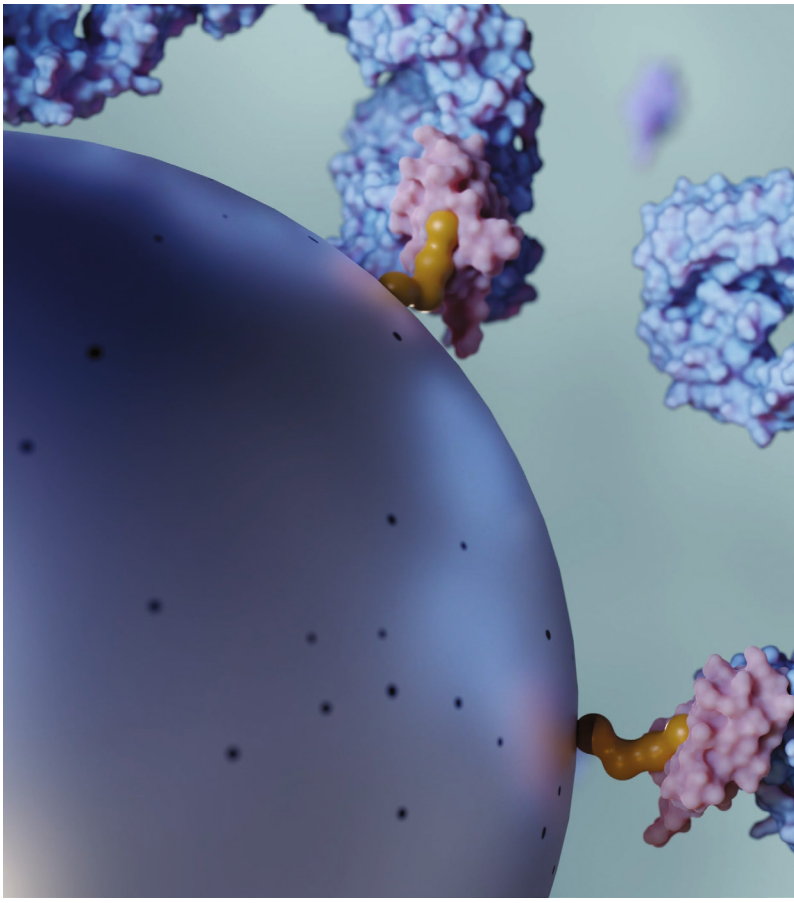
In the track focused on cell-based immunotherapies, Steven Quistad, Senior Applications Scientist, DNA Script, discussed how to rapidly assemble genes in a laboratory using automated enzymatic oligo synthesis. To demonstrate the utility of the company's SYNTAX system in gene assembly, the 1.7 kb Influenza A hemagglutinin gene was used as a model system. Three double stranded DNA (dsDNA) blocks were generated from EDS-synthesised ssDNA oligos using the PCA approach followed by error correction and the dsDNA blocks were then assembled using a commercially available kit, transformed into BL21 competent cells and colonies were selected for Sanger Sequencing confirmation.

Reflecting on PEGS Europe 2023

Molecular Partners, a clinical-stage biotech company developing a new class of custom-built protein drugs known as DARPin therapeutics, presented several of its programmes, focusing on the multiple ways Molecular Partners has designed DARPins to activate the immune system against cancer only under certain conditions. This conditional activation is intended to focus immune attack more specifically against tumour cells and minimise damage to healthy cells, a major challenge for current oncology drugs and development efforts.

Meanwhile, OSE Immunotherapeutics, a clinical-stage biotechnology company working in immuno-oncology and immuno-inflammation, presented scientific updates featuring the latest progress on the company's research programmes in immuno-oncology, namely CLEC-1 (novel myeloid immune checkpoint), CYTOMASK, a new and innovative CIS-demasking cytokine linker technology, BiCKI-IL-7 (bifunctional therapy targeting PD-1 and IL-7), and Tedopi (T-cell epitope-based cancer vaccine).

From a product perspective, RedShiftBio had the Aurora protein analyser with them in Lisbon this year. With a small sample, Aurora fully and rapidly characterises biomolecules of interest, detecting structural changes early and more accurately than traditional spectroscopic methods. In their poster presentation, RedShiftBio made a structural comparison of the matrix metalloproteinases using microfluidic modulation spectroscopy (MMS), illustrating how characterising biomolecules with MMS can save both time and money.



Molecular Devices was also in attendance introducing the plasmid mini-prep starter bundle, which is scaling plasmid manufacturing with streamlined automation. Meanwhile, Azenta was ensuring attendees could learn more about the company's GENEWIZ multiomics and synthesis solutions both on their booth and in a presentation by Crystal Richardson on innovative antibody discovery workflow, leveraging AI to prioritise leads.

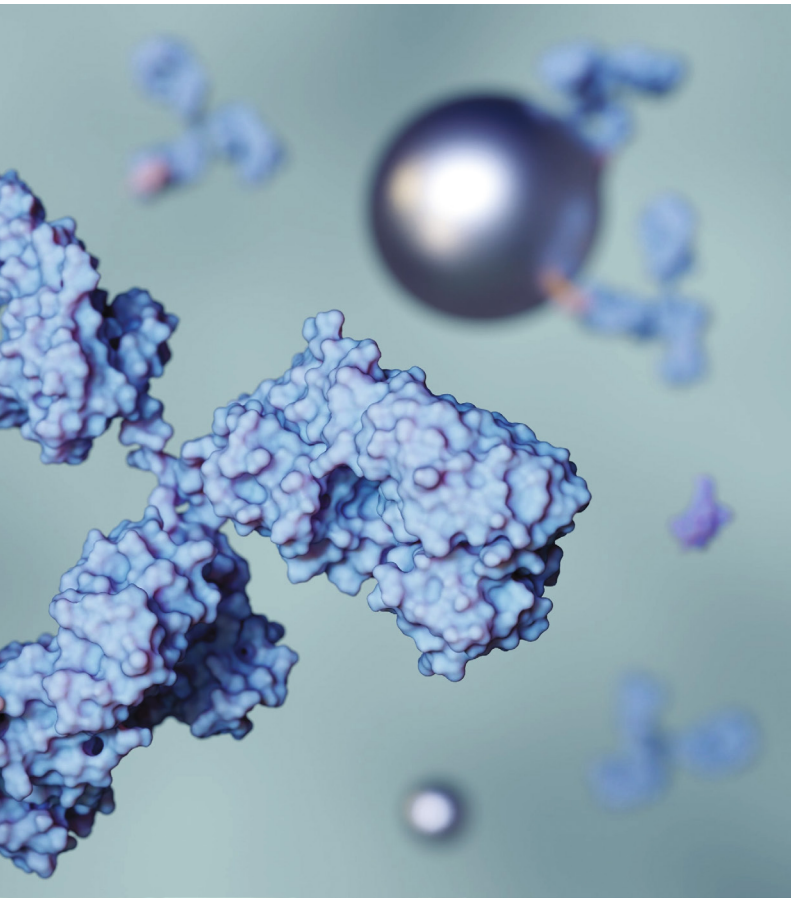
The Halo Labs team was available to share insight into Aura, which enables the tool to enable full and accurate analysis of SVPs therapeutic end-products. Moreover, in the session on advances in analytical techniques and approaches, Paul Dyer, Field Application Scientist, Halo Labs, presented on the possibilities of total particle analysis with Aura and the pathway to USP validation and product release.

Poster spotlight

Bio-Rad was in attendance not just to provide insight on the exhibition floor on the company's purification tools and antibody products, but also for two poster

presentations, which included: 'Development of IEX purification process for lentiviral vectors' and 'Chromatography purification of AAV8 using mixed-mode chromatography'.

Also contributing to the poster exhibit was Charles River Labs, with the following presentations: 'Supporting CAR-T cell therapy development from discovery to IND-filing', 'Bispecific antibody discovery platform for IND enabling studies', and 'Antibody-drug conjugate off-target



binding screen: Increasing the confidence in ADC safety during development'.

Promega had two posters from which to share insight, which included: 'Cell-based luminescent reporter bioassays for immunotherapies targeting macrophage effector functions', and 'Development of bioluminescent no-wash Fc gamma receptor binding immunoassay to guide the development of antibody therapeutics'.

The Absolute Biotech team was available to discuss custom services, as well as the company's comprehensive antibody reagent catalogue. They were also representing on the poster front, with a presentation on comparing potential bispecific formats comprising of trastuzumab and a humanized OKT3. The poster shows how the company systematically built and evaluated 17 bispecific designs, including a number of well-utilised formats, in order to find that Fc-containing formats and the placement of scFv can influence the expression dramatically, while discovering that interface stability for heterodimeric constructs is equally important.

Meet the exhibitor

Of course, an event such as this brings the opportunity to meet, greet, network, and learn from various exhibitors showcasing their work and recent milestones.

Sartorius was presenting at the event, featuring Field Application Specialist, Gail Calvert, who discussed leveraging integrated and advanced technologies for successful cell line development, the team was also at hand to outline solutions for single cell, clone and colony analysis, screening and isolation, live-cell imaging and analysis, as well as label-free biomolecular interaction analysis. Not to mention, Polypus, a French lab technology company acquired by Sartorius earlier this year, had expert Marine Houdou on hand to discuss modular DNA assembly to recombinant protein production at Polyplus, as well as poster presentations on how to improve protein production yields in mammalian cells through plasmid engineering and transfection optimisation.

Alongside a presentation by Jyotsna Venugopal, Director, Product Marketing, Telesis Bio, on automated solutions for overcoming synthesis bottlenecks in CAR-T cell therapy workflows, the experts at the company's booth provided the opportunity for attendees to find out how Telesis Bio's BioXp solutions heave enabled optimisation of CAR generation workflows, and the assembly of optimised CARs; generation of mRNA for T cell manipulation, enabling rapid candidate screening through transient modulation of cellular phenotypes; as well as automated overnight synthesis of lead candidates across biologics discovery workflows.

Sphere Fluidics' presence on the exhibition floor was bolstered by a presentation from Richard Hammond: 'Picodroplets for cell Line engineering: A novel automation approach'. Between these, the company was introducing the Cyto-Mine platform, which enables a step-change in speed and scale of working. In his presentation, Hammond showed how microfluidic-enabled picodroplets deliver integrated, user-friendly, automated workflows where millions of individual cells are assessed daily, and the best single cells selected – in an environment that maintains high cell viability and outgrowth.

Revvity was involved with both the event talks and the posters, as well as having a team of experts on the booth. Ana Rebocho, Manager, BioP R&D of Revvity, presented on accelerating biologic development programmes with a state-of-the-art CHO expression system within the session on automation and process optimisation in the 'Protein process development' track. In addition, the company presented three posters: 'Integration of next-generation transposon vectors with state-of-art host cell lines', 'Application of gene editing technologies to improve biotherapeutic manufacturing', and 'CHOSOURCE ADCC+ cell line for enhanced therapeutic potency'.

By visiting the Icosagen booth, attendees had the opportunity to hear more about the company's clinical and preclinical competencies can translate research ideas into functional, GMP-ready proteins. Additionally, Icosagen CSO Mart Ustav Jr was presenting on how cancer cells react when deprived of glucose. Meanwhile, the Malvern Panalytical booth gave attendees the possibility to speak to company experts, as well as to see how products work – including the opportunity to play Malvern's Kahoot game.

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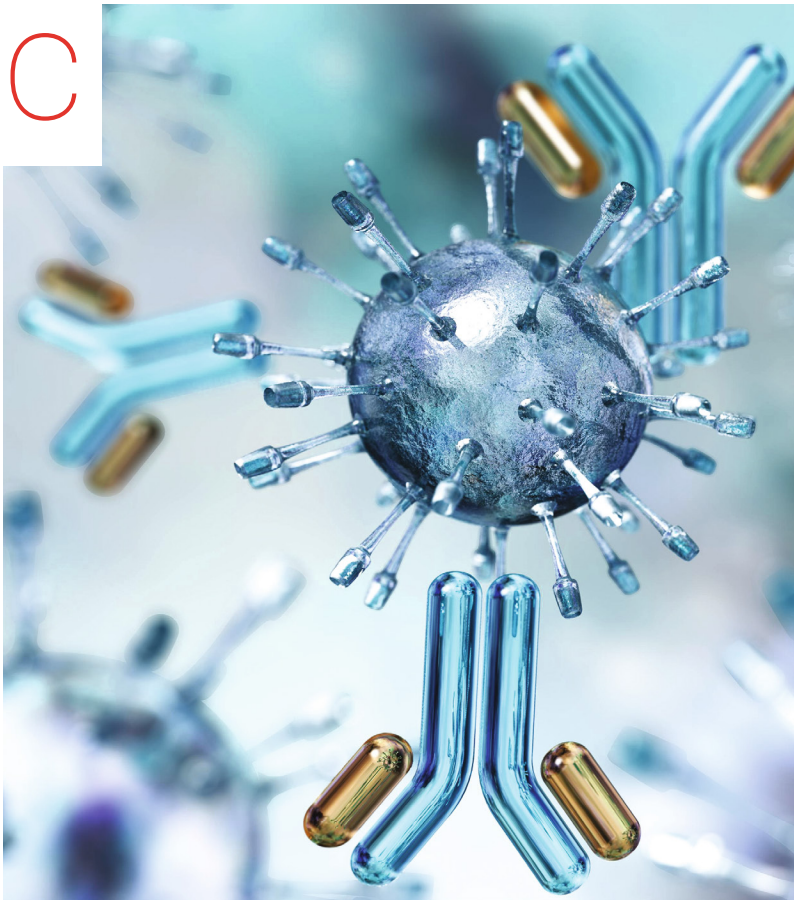
Therapeutic antibody potential in 2024



DDW's **Megan Thomas** speaks to industry experts and thought leaders about the potential for therapeutic antibodies in 2024.

Many of the best-selling drugs in 2023 were monoclonal antibody (mAB) therapies, including Keytruda (pembrolizumab), Humira (adalimumab), and Dupixent (dupilumab)[1]. This won't come as a surprise when you look at industry milestones achieved in 2023 and looking ahead, this shows no signs of slowing down.

Artificial intelligence (AI)

AI is on everyone's minds as we head into 2024; of course, this is across not just the drug discovery spectrum but is particularly relevant to therapeutic antibodies.

This is reflected in collaboration and investment patterns; in 2023, Antiverse, a biotechnology company developing a computational antibody drug discovery platform, raised seed funding totalling £1.4 million, comprising new investment and match funding from the UKI2S Innovate Accelerator. The company also partnered with a top 20 pharma company and has been successful in identifying antibody candidates for a target of interest, with greater diversity (2.3x) and accuracy compared to alternative bioinformatics pipeline selection methods.

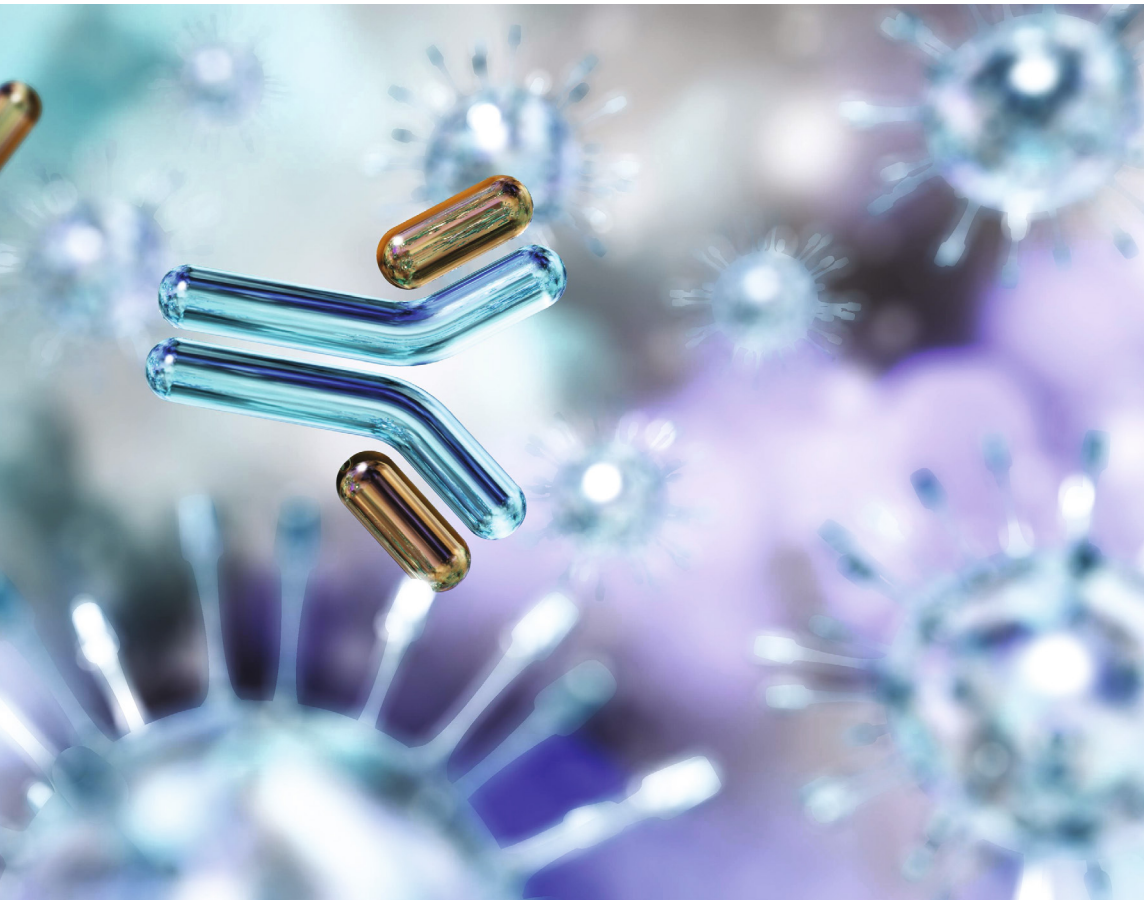
Ben Holland, Co-Founder and CTO of Antiverse, notes that AI and machine learning now touch 10% of drug discovery projects. He says: "Developability prediction is often used in antibody development to reduce wet lab experiments and accelerate the drug discovery process. We anticipate developability prediction becoming widespread and somewhat commoditised, but with a continually rising bar, it will remain an important technology."

AI's significance is also evident in the science, where immuno-oncology company Aulos Bioscience recently revealed interim results from an ongoing Phase I/II trial of an AI-designed monoclonal antibody (mAb), AU-007, in solid tumours. According to Aron Knickerbocker, Aulos Bioscience's Chief Executive Officer, the new data supports the company's belief that AU- 007 offers a novel mechanism of action among interleukin-2 (IL-2) therapeutics in development, as demonstrated by AU-007's pharmacodynamic and safety profile to date.

> **Research will likely focus on expanding applications in infectious diseases and autoimmune disorders.**

Advancing mAbs

There has been a steep growth and expansion curve when it comes to mAbs, especially when considering the FDA approvals that occurred in 2023, including examples such as FDA clearance to Transcenta to proceed with its TranStar 301 global Phase III pivotal trial of Osemitamab (TST001) for gastric cancer, as well as the FDA Fast Track designation for Alentis Therapeutics' investigational mAb, ALE.C04, which is indicated to treat patients with recurrent or metastatic CLDN1-positive head and neck squamous cell carcinoma (HNSCC). Not to mention, Pfizer's Elrexfio (elranatamab- bcmm) was granted accelerated approval for the treatment of adult patients



with relapsed or refractory multiple myeloma (RRMM), and FDA approval of AstraZeneca's Beyfortus (nirsevimab-alip) for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants born during or entering their first RSV season.

Looking forward, Lia Sylvestri, Director Customer Experience & Engagement, TrakCel, notes that significant advancements in mAbs research are anticipated with leading companies, such as Roche, Regeneron, and Eli Lilly, who are expected to drive breakthroughs in precision medicine, tailoring mAbs for diverse diseases. She says: "Innovations include next-generation antibodies with improved efficacy and reduced side effects. Research will likely focus on expanding applications in infectious diseases and autoimmune disorders."

Meanwhile, Richard Hammond, CTO of Sphere Fluidics, comments that the development of mAb-based therapies has rapidly taken off within the last few decades, which he owes to advances in molecular biology and high-throughput screening technologies. These enable researchers to better manipulate biological molecules or identify the best candidates to progress to the next stage of development.

> **"Expanding synthetic biology capabilities are enabling the development of novel mAb-based drug candidates."**

Hammond says: "Many of the most popular drugs in 2023 are mAb-based therapies, which we predict will continue in 2024. We also predict that the number of new candidate drugs being identified or entering clinical trials that are mAbs will also increase. This is due in part to advances in antibody discovery platforms, such as ours that use droplet-based microfluidics technology to streamline and accelerate the initial screening process.

"Expanding synthetic biology capabilities are also enabling the development of novel mAb-based drug candidates, such as bispecific mAbs and conjugated mAbs. Increasing recognition of the potential and applicability of mAb-based therapies is being reflected through the increased funding and number of research projects, which we predict will continue to rise well beyond 2024 in line with global demands. For example, the rising incidence of cancer – a disease where treatment using mAb-based therapies is increasingly appropriate – will continue to drive market growth, as well as the need to develop novel therapies for diseases where therapeutic options are limited or are difficult to target."

Adoptive T cell therapy

Carole Nicco, CSO of BioSenic, adds that mAb immunotherapy is the most widely used approach and has achieved tremendous success. She says: "Adoptive T cell therapy (ACT), particularly T cell-based transplantation, is attracting increasing attention and is advancing rapidly since the FDA approval of CAR-T therapy for the treatment of relapsed/refractory acute lymphoblastic leukaemia and B-cell malignancies.

"Other ACTs such as TIL, TCR, NK cell, Treg, and MDSC therapies are now emerging. High response rates have been reported for both mAb and CAR T cell cancer therapy; however, treatment refractoriness and disease relapse still occur and represent an ongoing clinical challenge. Although several issues regarding ACTs, such as safety, efficacy and persistence, need to be addressed, ACTs are being continuously produced and an increasing number of commercial products are being approved, mainly due to their advantages such as simple composition and controllable scalability. In the future, the combination of CAR T-cell therapy with local small molecules, such as BioSenic's arsenic trioxide, may be a combinatorial strategy to overcome the limitations of each monotherapy."

Originally published in DDW Volume 25 – Issue 1, Winter 2023/2024 – Therapeutic Antibodies Guide

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1 https://www.ipharmacenter.com/post/best-selling-drugs-of-2023-top-10-drugs-by-revenues-best-selling-pharmaceuticals-ipharmacenter

Finding the North Star of therapeutic antibodies

Katie Abouzahr is the Vice President, Autoantibody Portfolio and Maternal Fetal Disease Area Leader at the Janssen Pharmaceutical Companies of Johnson & Johnson. She speaks with **Megan Thomas** about the future for Janssen's investigational medicine nipocalimab and antibody therapeutics at large.

A day in the life

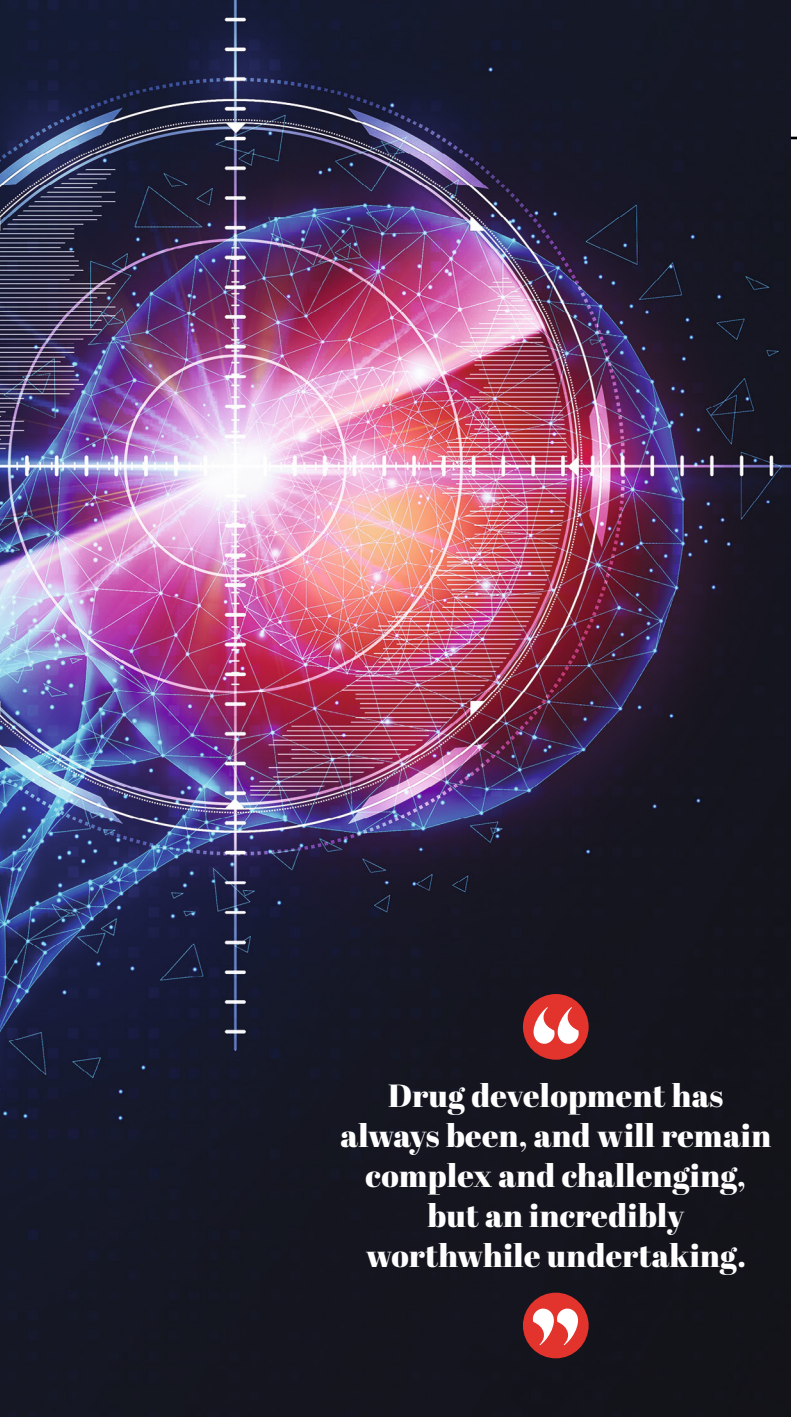
On a day-to-day basis, Katie Abouzahr is accountable for and leads the development globally of all the assets in Janssen's Autoantibody portfolio in immunology. Notably, that includes nipocalimab. This is a fully human monoclonal antibody (mAb) which selectively binds to the FcRn receptor with high-affinity and blocks it, thus leading to a decrease in IgG autoantibodies. Nipocalimab, according to Abouzahr, is currently the only FcRn being studied in all three segments of autoantibody-driven disease. Moreover, Janssen has ten prioritised indications across maternal foetal, rare autoantibody, and prevalent rheumatology.

Abouzahr explains: "In terms of day-to-day life, it varies significantly depending on what the needs are across the programme, or where we are in specific areas. I try hard to prioritise my efforts as to where I lean in with the team. It ranges from setting a strategic direction, all the way through to successful operational delivery of a specific programme or indication. I am constantly in contact with the team to make sure I'm on top of the latest status of our programmes, I'm thinking about next steps, and as you can imagine, it's a mixture of meetings in person, virtually, emails, conferences... So, the full gamut, which I love, because no day is ever the same. But if I think about what is the North Star, or what guides where I put my time, it's: how do we bring this new medicine to patients in need? Is what I'm doing now going to materially enable that?"

Innovation and evolution

Abouzahr says that we are seeing incredible advancements in the development of therapeutic antibodies to treat diseases, which she attributes to a growing understanding of the immune system and its mechanisms, which we can bring together. She says: "At Janssen, we're fortunate that we're building on a leadership that we've created over the last couple of decades of treating immune-mediated diseases. What I think we're doing in the portfolio that I lead is applying that deep understanding and leadership to addressing this specific area where there's so much unmet need, which is autoantibody-driven diseases."

These, she explains are caused by pathogenic antibodies and tend to be IgG's that are made



> **Drug development has always been, and will remain complex and challenging, but an incredibly worthwhile undertaking.**

by one's own body and attack organs and tissues. They also occur in pregnant individuals, called alloantibodies, where maternal alloantibodies can cross the placenta and cause harm to the developing foetus. She adds: "It's a version of your immune system responding abnormally, so instead of turning on viruses, bacteria is turning on oneself, and it can be lethal. There are approximately 80 chronic autoimmune or acute alloimmune conditions. They span rare and prevalent. As I mentioned, they're across three pillars in terms of how we think of them – maternal foetal like haemolytic disease of the foetus and newborn (HDFN), rare autoantibody like myasthenia gravis (MG), prevalent rheumatology like rheumatoid arthritis (RA). But maybe the most important thing is the approximately 240 million people – that's 2-3% of the world's population – of which the vast majority have limited safe, effective, approved, let alone targeted treatments. If I think back to the North Star, that's how the team really approaches this."

In terms of advancing how we think about doing this, Janssen has a pathway-centric development strategy, which takes a deep understanding of the immune system and of the diseases and uses it to identify a common pathway, then the team pursues medicines that can modulate that pathway and can potentially treat multiple diseases with one therapy. Abouzahr says: "The one that's probably front of mind for most people is nipocalimab, which is our anti-FcRn pathway approach to around ten indications that are autoantibody-driven. Nipocalimab is a neonatal FC receptor blocker. Actually, ours is uniquely engineered to bind really tightly to the FcRn receptor, which leads to rapid, deep, sustained lowering of IgG and auto and allo antibodies. That allows you to go after auto and alloantibody-driven conditions. Partly because of the way nipocalimab binds so tightly at different pHs, it is the only drug currently being studied in maternal foetal, rare autoantibody and prevalent rheumatology. There are so many advancements and all of that allows us to really try and bring new medicines forward for patients who need it the most."

Opportunity and the future

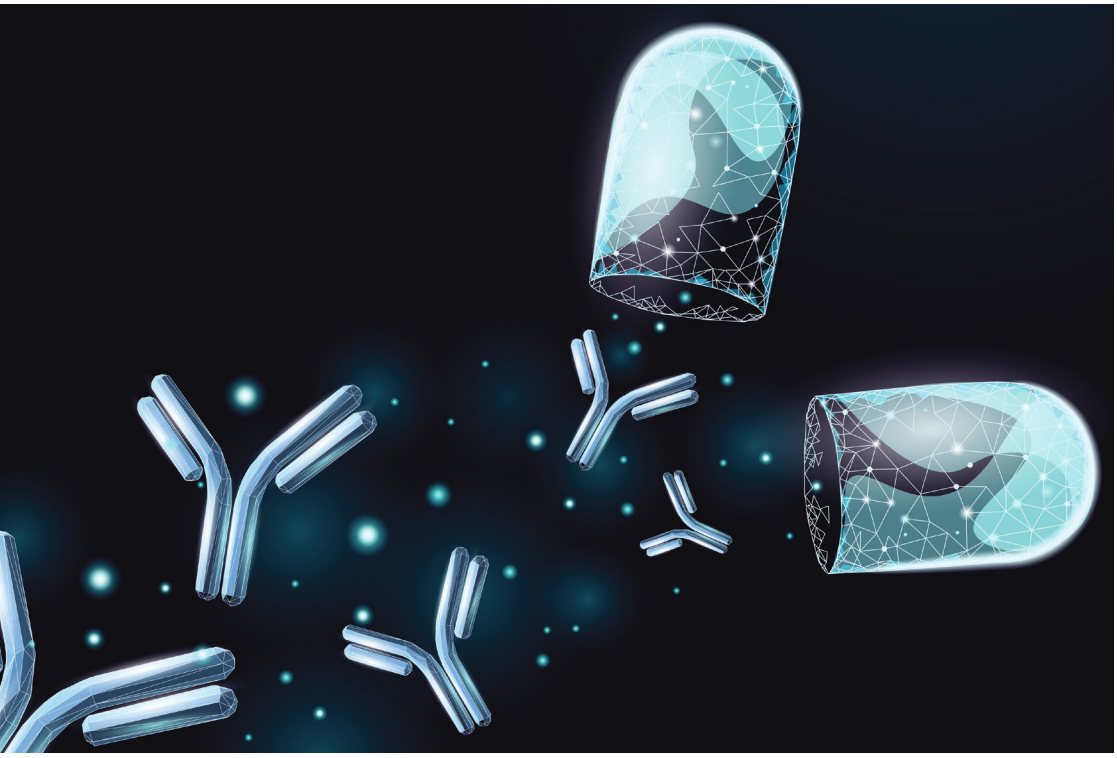
Thinking about where we are now and where we want to get to for the antibody market, Abouzahr explains: "For most autoantibody-driven diseases, physicians and patients end up with approaches that are perhaps nonspecific, haven't been developed specifically for that indication, or have insufficient or inadequate efficacy and/or safety and tolerability challenges. So, what we really want is for treatment to be safe, effective, approved and targeted. When you're trying to think about what the opportunity is, it's across all four of those, and so back to our North Star: how can we bring this forward for patients?"

From a programme perspective, there are two opportunities that are particularly exciting for Abouzahr. The first, is that Janssen has the only experimental therapy in development for the treatment of alloimmunised pregnant adults at risk of severe HDFN, an immense unmet need for women and their families which, in severe cases, can result in foetal demise. Abouzahr says: "We are really excited about the potential for nipocalimab here, building on some of the early results that we've disclosed already."

The second cause for excitement is at the other end of the spectrum. Abouzahr comments: "Moving from something ultra-rare with no treatment options to something prevalent, where there are a huge number of patients who, despite advanced therapy, are not experiencing remission... Here, I'm talking about patients with moderate to severe rheumatoid arthritis, where again, nipocalimab is the only FcRn in development there. We look forward to disclosing some results at the end of the year. So at either end of the prevalence spectrum, there is so much opportunity and so much excitement for what we might be able to do."

The potential of antibody engineering

"Antibody engineering has a transformational effect on drug discovery and how we treat diseases," says Abouzahr. She continues: "If you just think about some of the evolution, even just looking at Janssen really transforming treatment paradigms. I guess if I look ahead to what's next, what we're starting to see and again embodied a little bit in nipocalimab is a move towards restoring immune homeostasis and immune balance instead of just broad immune suppression. So, for example, nipocalimab is a relatively targeted therapy that takes out circulating IgG and autoantibodies, but it doesn't impact wider immune system processes. So, it's more about restoring homeostasis, and it's a more targeted approach. So that, I think, is the first place that we're really thinking about what's next."



Another place is treatment modalities. Abouzahr continues: "Typically, these have been, in the antibody space, injectable monotherapies. But we're starting to look ahead to the full range of modalities. So novel tissue directed and systemic orals, combination therapy to really get at those sorts of patient populations who haven't yet responded to previous advanced therapies, like in inflammatory bowel disease (IBD). So, I think those are some of the things that we've got to look forward to, ultimately in the service of patients and going back to: safe, effective, targeted, approved."

Tailoring to a disease

So, where is the mAb discovery and analysis market heading? Abouzahr reiterates that, as we get better understanding of autoantibodies, we continue to get more targeted. She said that she thinks therapies with very high specificity and an affinity for specific targets are where we are heading. "With nipocalimab, for example, the goal is to take out the autoantibodies, but wider immune function is maintained. I think that is a way of bringing precision and effectiveness. If I was a patient, that's what I'd want. I'd want something more tailored to my disease."

> **What we really want is for treatment to be safe, effective, approved and targeted.**

There is even greater ambition with precision medicine. Abouzahr says: "We talk about it, but I do think we're getting there with these personalised therapeutic approaches, where again, you're tailoring your treatment, not only now to a disease but to specific patients who may have that disease, who may have specific variations in their genes or the environment or how the disease manifests in them, thinking about biomarkers and things like that. You're narrowing in on what you can do for patients in a more targeted, effective way, specifically approved for their condition."

The next ten years

At the most macro level, the main drivers and challenges over the next ten years will be the standard challenges of drug development, according to Abouzahr. She says: "It's complex, it's complicated – as it should be. We should be doing this in a judicious, careful, thoughtful way that is appropriately challenged. We have this immense drive to bring medicines to patients but there has to be balance with doing it thoughtfully and carefully. Drug development has always been, and will remain complex and challenging, but an incredibly worthwhile undertaking."

She continues: "As we move into some of the diseases that haven't been studied before, which is, a lot of the time, where the unmet need is, it becomes challenging to be innovative. New indications are sort of 'uncharted' by definition, and I think that will increase as we go forward, be it in something new and ultra-rare, or in something where we're moving towards the patients who haven't yet responded to advanced therapies."

Abouzahr says that ultimately, it's about repeatedly asking why her team gets out of bed each day and remembering it's about helping those with HDFN, or individuals affected by something like systemic lupus erythematosus, which disproportionately affects women and people of colour. She adds: "If you keep in mind that you could bring forward safe, effective, approved, targeted treatment options, then no matter how complex it is, or how challenging, you will get there in the end."

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Biography:

Katie Abouzahr, MD, is Vice President, Autoantibody Portfolio and Maternal Fetal Disease Area Leader at Janssen Research and Development (R&D). Prior to her work at Janssen, Abouzahr served as a Principal at the Boston Consulting Group in London and Philadelphia for 12 years. Prior to that, she practiced as a medical doctor for the National Health Service (NHS) in London.

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