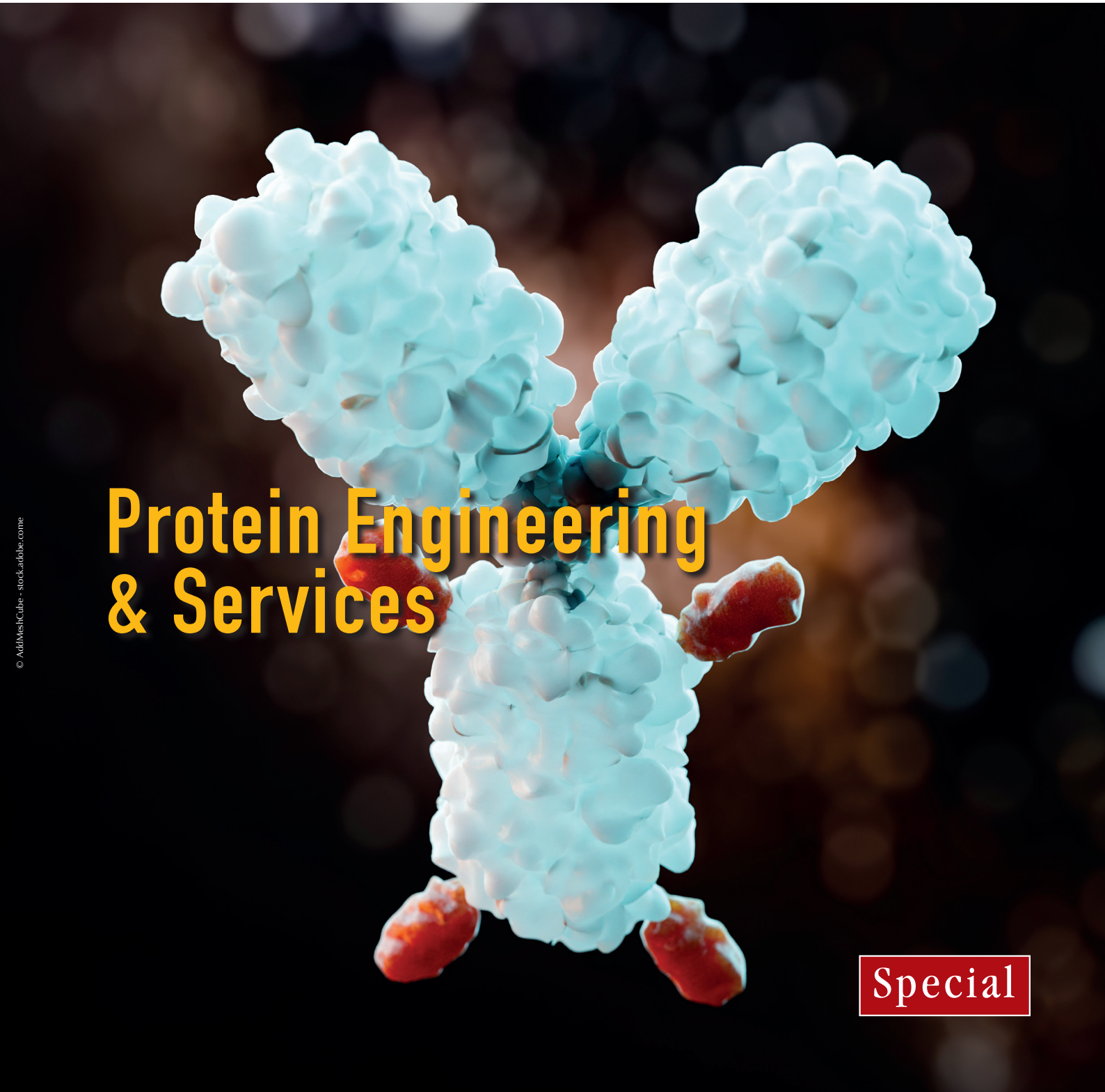
European Biotechnology

Winter 2024



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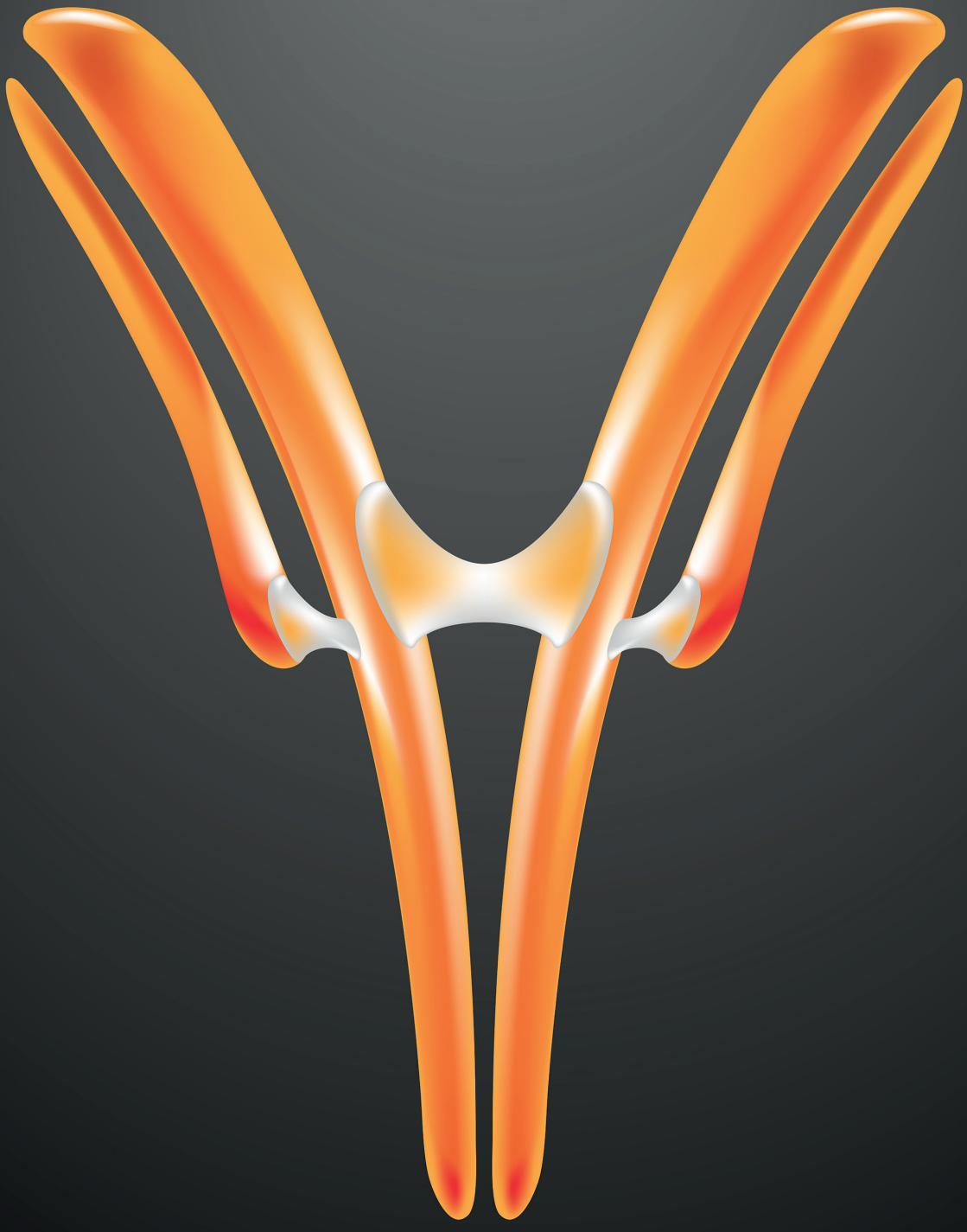

New proteins on the block

PEGS EUROPE 2024 Monoclonal antibodies still dominate the US$417bn biologics market. After decades of development, however, improved antibodies and protein formats with better target selectivity and safety profiles are now hitting markets and pipelines. A range of bispecific antibodies and antibody-drug conjugates – along with CAR-Ts, TCR-RTs and NK cell-based immunoreceptor constructs – were in focus at the PEGS Europe Summit.

Since the first antibody drug (muromonab-CD3) was approved back in 1986, monoclonal antibodies (mAbs) have emerged as the dominant class in the global US$417bn market for biologics. At the end of 2023, sales stood at more than US$230bn. However, as tumours – in addition to autoimmune diseases still one the most important application fields of mAbs – are moving targets, newly engineered antibody and engineered protein formats that unite complementary cell-killing mechanisms in a single molecule have been developed, approved and are increasingly leaving clinical pipelines for the market. They include refined bispecific antibodies, antibody drug conjugates (ADCs) and targeted radiopharmaceuticals, as well as immune-receptor-based cell therapies such as CAR-T and TCR-T cell therapies.

Every year at the PEGS Europe Summit, the CSOs of bio/pharma companies provide a detailed overview of newly developed therapeutic modalities, and thus an outlook for the future. This year in Barcelona, the 16th summit helped clarify why the approval of bispecific antibody formats has increased dramatically (13 out of 18 approvals in the past three years) and why improved ADCs, CAR-Ts, TCR-Ts and new modalities are entering the market. The freshly engineered formats promise to reduce current problems of bispecific antibody and T-cell therapies such as cytokine release syndrome (CRS), neurotoxicity, and on-target/off-tumour toxicity. In addition, targeting two targets simultaneously increases selectivity, and allows drug developers to combine complementary cancer-killing mechanisms that could reduce resistance to cancer therapies and improve efficacy.

YEMI ONAKUNLE Founding Director and CEO, Mabswitch Inc., Cambridge, USA

? How can toxicities and T-cell exhaustion that occur in all T-cell-based therapies be avoided?

! *Mabswitch's remote-controlled antibodies offer a novel approach to enhance the efficacy of antibody-redirected therapies – such as CAR-T cells, T-cell engagers, and ADCs – for treating devastating diseases like cancer, autoimmune disorders and chronic infectious diseases, all while minimising side effects.*

"Based on recent therapeutic progress, ADCs and bispecific antibodies (bsAbs) represent the fastest-growing class of therapeutic antibodies in development and have been a major driver of dealmaking in the biopharmaceutical industry in the past years," emphasised Dr Christian Klein at the PEGS summit, which took place from 5-7 November. The patent champion (240!) in protein engineering, who moved to early-stage investor Curie.Bio in the summer after 22 years at Roche pRED (see p. 3, p. 38) started with a brief summary of the 14 bispecifics (and 17 – still monospecific – ADCs on the market) approved until December 2023. But he quickly turned to what's new, interesting and probably a business case. And there is a lot of ground to cover, as around 50% of bispecific antibodies are already in late phase testing (Phase II or III, see Fig. 1, p. 14).

New age for bispecifics

According to Klein, T-cell engagers (TCEs), together with cancer immunotherapies, now account for almost 80% of the bispecific antibodies clinically developed to fight cancer. They are also increasingly used in indications beyond haematological

cancers, namely solid tumours and autoimmune diseases (TCEs and dual-ligand blockers). Dual-ligand inhibitors such as faricimab (VEGFxAng2) from Roche, which was approved by the FDA in 2022 for the treatment of wet age-related macular degeneration (AMD), have already found their way into ophthalmology. And Sweden's BioArctic AB is working on an advanced version of Roche pRED's transferrin receptor-mediated brain shuttle technology, which was presented for the first time at the PEGS Europe Summit. According to data revealed in Barcelona, the brain transporter platform, which was licensed to Esai last year, was able to increase brain exposure to an anti-amyloid beta antibody by 70-fold. Bispecific antibodies in the obesity field have also already been the subject of licencing agreements, such as the as yet unnamed dual activin type IIA and IIB receptor modulator from Swiss SixPeaks Bio AG, for which AstraZeneca has an option since May.

Approvals in 2024

A total of three "classic" TCEs have been given the green light by the regulatory authorities this year, including one for solid tumours. In May, Amgen's DLLxC3-BiTE format tarlatamab-dlle got FDA approval as a second-line treatment for extensive stage small cell lung cancer (ES-SCLC). In August, Regeneron's previously FDA-rejected, hinge-stabilised Fc-binding-reduced CD20 x CD3 bispecific IgGπ antibody odronextamab received EU approval as a third-line therapy for patients with follicular lymphoma and diffuse large B-cell lymphoma. Both share the CD3-related (CRS) toxicity of first-generation products. The very first bispecific T cell engager (EpCAM xCD3) Removab (catamaxumab, Trion Pharma) against malignant ascites (approved 2009, withdrawn 2014) is set to be reapproved in the EU and marketed by Lindis Biotech/Pharmanovia later this year. There were also two approvals for candidates with an alternative design:

- At the end of November, Zymeworks Inc's/Jazz Pharmaceuticals Inc's biparatopic HER2 signalling blocker zanidatamab-hrii got the FDA stamp. Binding of zanidatamab with two different extracellular epitopes on HER2 (D2 + D4), previously targeted separately by Roche's blockbuster HER2 antibodies Herceptin and Perjeta, results in internalisation leading to a reduction of the receptor on the tumour cell surface. It unites three tumour cell-killing mechanisms in one antibody: CDC (complement-dependent cytotoxicity), ADCC (antibody-dependent cellular cytotoxicity) and ADCP (antibody-dependent cellular phagocytosis). According to Klein, combining MoAs that are not accessible to monoclonal antibodies exactly is what makes some of the novel bispecific constructs so interesting.
- Another new approach, pioneered by Chinese biotech Akeso Biopharma Co. Ltd, is combining different immune checkpoint inhibitors in a bispecific antibody. Back in 2022, Akeso Bio received NMPA approval for the very first-(PD1 x CTLA4) drug in this new class of cancer immune therapies. Interest in a bispecific combination that unites checkpoint inhibition with angiogenesis through PD-(L)1xVEGF bispecific antibodies blew up after Akeso Bio and Summit Therapeutics celebrated a first-time victory of ivonescimab (SMT112) over MSD's US$15bn per year blockbuster pembrolizumab in a head-to-head Phase III trial. That was followed by approval of the drug in China as a first-line NSCLC treatment. The results – objective response rates were 50% with ivonescimab versus 38.5% with pembrolizumab, disease control rates were 89.9% and 70.5%, respectively – is still sending shockwaves through the immuno-oncology industry (see p. 15).

In the field of haematological and solid cancers, what is still the dominant application field (73% solid tumours, see Fig. 1)

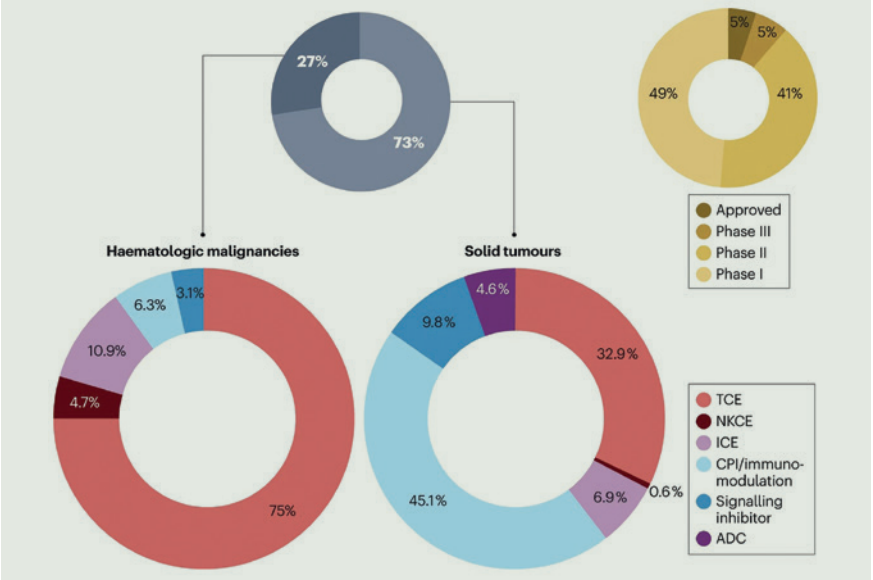

Fig. 1: According to estimates of the Antibody Society, about 300 bispecific antibodies are in clinical evelopment, mostly in oncology, with 73% of them against solid tumours. The first approved drug in that class (Removab, 2009) from German Trion Pharma (EpCam x CD3) against malignant ascites was a T-cell engager (TCE). TCEs are artificial bispecific antibodies that attach to tumour-associated antigens (TAA) with one of their binding regions and to the CD3 receptor on T killer cells with another, thus redirecting T cells to kill cancer cells. Most TCEs today are IgG-like antibodies, because these are more stable compared to BiTEs, which consist of two single-chain variable fragments (scFvs) of different antibodies. Other upcoming modalities include bispecific ADCs, multispecific antibodies, and bispecifics that bind to two different targets or those that trigger decay of tumour-driving receptors.

of the currently more than 50 different formats of bispecific antibodies, dual receptor tyrosine kinase blockers and biparatopic constructs such as zanidatamab are only one approach that will increasingly see clinical uptake. The overall goal of all developers of new T-cell engaging approaches, bispecific ADCs etc. is to increase tumour selectivity, eliminate tumour escape and reduce dose-limiting systemic toxicities. Also to hinder the T-cell exhaustion that often leads to relapse or non-responsiveness to redirected T-cell therapies. Several strategies discussed at PEGS Europe by start-ups and biopharma companies address this problem.

Early-stage approaches

Yemi Onakunle, CEO of Mabswitch Inc (Los Angeles), presented a completely new technology in Barcelona that allows switching the T-cell binding affinity. According to him, this is instrumental to ameliorate TCE and CAR-T cell-therapy intrinsic toxicities caused by T-cell hyperactivation and chronic antigen stimulation. What he called "remote control" of an antibody's affinity is achieved by inserting a universal calmodulin-derived allosteric modulator domain between the two protein domains (VH/VL), which affects the molecular geometry of the antigen binding site of the antibody. The modulator – or "switch" – can be modulated itself electrostatically by a range of small molecules that can be added or removed. Onakunle showed data from Off- and On-switches for TCEs, CAR-Ts, ADCs or protein purification applications that altered the affinity of antibodies by two orders of magnitude. The universal allosteric affinity-switch worked independently of the paratope. The approach of the three-year old start-up, co-founded by Phage display co-inventor Stefan Dübel, enables both increased and decreased affinity in antibodies, offering a tunable strategy to enhance CAR T cell or T-cell engager safety and efficacy in patients.

Other approaches aim to circumvent T-cell-born safety issues by using alternative effector cells, namely NK or so-called MAIT cells. Simon Plyte, CSO of Biomunex Pharmaceuticals SA (Paris), said using an abundant tissue and tumour resident subset of cytotoxic non-conventional T cells that make up 20% of the T cell population could significantly widen the therapeutic index of T cell therapies. While the proprietary, bispecific BiXAb antibody-mediated redirection of these MAIT cells (Mucosal Associated Invariant T cells) to TAAs lead to the elimination of cancer cells with a potency identical to that of classical CD3ε T-cell engagers, MAIT engagers triggered neither cytokine release syndrome nor regulatory T-cell activation, because they are activated through binding to the iTCR. According to data shown by Plyte, tumour-resident MAIT cells are able to eliminate autologous tumour cells in a MAIT-engager mediated manner, and can infiltrate and kill tumour cells in patient-derived 3D models of cancer.

Another approach, chosen by French Innate Pharma SA, which also has fourth-generation ADCs in its portfolio, is to circumvent the T-cell-specific problems by using NK cells that neither induce CRS nor activate $CD25^+$ regulatory T cells. The company's tetraspecific B and NK cell engager IPH6501 exhibited higher anti-tumour efficacy and lower systemic toxicity than CD20-targeting TCEs. The candidate currently undergoing Phase I/II trials, engaged NK cell-activating receptors (NKp46 and CD16), the CD20 TAA on B cell blasts and includes an IL-2 variant designed to avoid binding to CD25, limiting Treg activation and potential IL-2 related side effects (see p. 70).

Local activation

In addition to these innate cell engagers, approaches in which probodies are first activated in the tumour were also discussed at PEGS Europe. Here, the binding sites are initially masked sterically or by attaching protective groups, which are cleaved off by TME specific proteases. Or they are engineered to be active only at acidic pH or high ATP concentrations. An alternative approach for dual tumour targeting at an early stage is based on the tumour-specific composition of a functional CD3ε antibody fragment consisting of two bispecific antibodies with split CD3ε binding moieties. These units must be designed to be inactive and circulate as separate units so that they are activated only after binding of the tumour antigen and

Shockwaves

While Chinese Akeso Biopharma Co. Ltd/ Summit Therapeutics conducts clinical trials with its heterobiparatopic (PD1x-VEGF) antibody ivonescimab across 16 indications, competitors have invested huge amounts of money to fill the hole in their pipelines. In mid-November, German BioNTech SE made an US$800m + US$150m tender to acquire its Chinese partner Biotheus Inc in order to gain control of its cancer candidate PM8002 (now BNT327), a VEGF x PD-L1 bispecific antibody in Phase I/II testing with a claimed "similar design" to ivonescimab. Some days later Merck Sharp & Dohme, which markets pembrolizumab, hit back by announcing it will pay US$588m upfront plus up to US$2.7bn biobucks to acquire the global rights to Chinese LaNova Medicines' Phase I-ready PD-1x VEGF bispecific antibody LM-299. The bispecifics race could heat up if MCT11 turns out to be safe and efficient in clinical trials. Finally, in late October, four-year old Ottimo Pharma left stealth mode, announcing it will start clinical testing of a PD1 x VEGFR2 bifunctional antibody in early 2025. This latest series of deals – as previously in the field of ADCs, where Chinese biotechs sit on 42% of the pipeline – really shows that science is about international collaboration, not trade barriers. At the largest pharma event in Europe, the CPHI in Milan, a survey of 280 biopharma/CDMO/CRO decisionmakers revealed that a majority are opposed to blocking collaboration between US/Chinese biotechs through draft US laws. ■

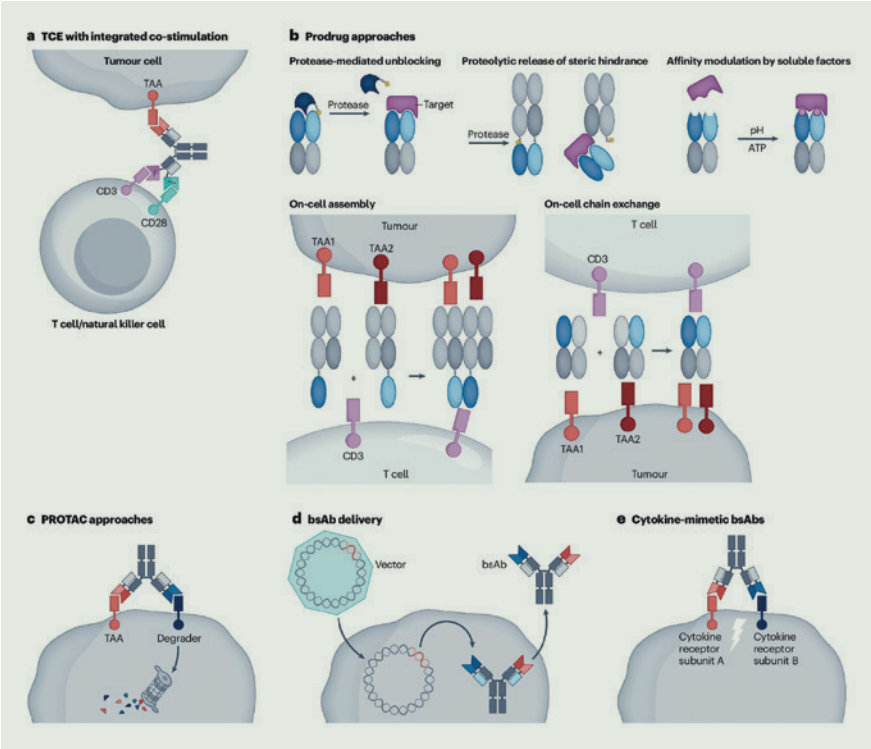

Fig. 2: Emerging concepts in the field of bispecific antibodies. A. Multispecific antibodies that i.e can simultaneously activate two co-stimulators of T-cell receptors (TCRs): CD3 and CD28. B. Different approaches aim to prevent off-target toxicity and boost tumour selectivity by using bispecific antibody prodrugs that are exclusively activated through enzymatic, pH- or binding-induced demasking when they reach the acidic tumour microenvironment (TME) or target site in the tumour. C. As many to-date undruggable pathogenesis drivers are not enzymes, their degradation through the proteasome has become a treatment option, even to prevent the expression of proteins that trigger tumour resistance. Bispecifics target these tumour proteins and ubiquitin-ligase induced tagging for specific degradation of such cancer drivers. D. Systemic side effects of bispecific antibodies or TCEs can also be ameliorated via gene-therapy delivery, i.e. into CAR-T cells. E. Bispecifics that bind to cytokine receptors can also be used to trigger cell activation.

subsequent *in situ* assembly. However, it is tricky to produce the monomers because they tend to aggregate in solution.

At PEGS Europe, Thomas Spreter von Kreudenstein, Senior Director Protein Engineering and Multispecific Antibody Technologies at Zymeworks, presented a new conditional masking approach for Zymeworks' cIL-12 cytokine fusion protein ZW270. Though IL-12 drugs have already shown the ability to turn 'cold' tumours 'hot', they also delivered poor responses – most likely due to toxicity and thus a low therapeutic index. After optimisation, an attenuated, masked IL-12 Fc (ZW270) showed anti-tumour efficacy in a humanised syngeneic mouse model in a dose range from 0.5 mg/kg-32 mg/kg, while reference mice with unmasked wild-type IL-12 showed a maximal tolerated dose of less than 0.05 mg/kg. Testing is ongoing.

ADCs and radio-DARPiNs

While the 13 approved antibody-drug conjugates (ADCs) enable the selective delivery of highly cytotoxic payloads linked to a tumour-targeting antibody with 50%-60% objective response rate on average, challenges such as drug resistance, tumour heterogeneity and treatment-related adverse effects continue to hamper the medical success of this drug class, which saw its first approval in 2000 with Pfizer's second-line CD33-positive AML therapy Gemtuzumab ozogamicin.

Different engineered ADC formats and – above all – new payloads were discussed at the PEGS Europe Summit, with the goal of widening the still too-narrow therapeutic index of the rapidly growing clinical pipeline (300 INDs this year, mostly in China, which holds 42% of it). New formats discussed included bispecific ADCs, conditionally active ADCs, immune-stimulating ADCs, protein-degrader ADCs and dual-payload ADCs. Premature payload release, poor tumour penetration, variable drug-to-antibody ratios and aggregation were the topics discussed most.

Joost Uitdehaag, Head of Biology at Crossfire Oncology BV, underlined the need for new non-chemical payloads, because these most common payloads limit the application of ADCs due to their high systemic toxicity. He highlighted kinase degraders targeting cancer-driving proteins, because the 80 approved kinase blockers would have better selectivity and are less toxic than anti-mitotics, tubulins and topoisomerase I blockers. He reported on a Phase I-ready novel cell cycle kinase degrader payload called CFON 18801, which was screened from 300 candidates with kinase and cell-based HIBIT assays, and its application as part of a Degrader-Antibody-Conjugate (DAC) to target metastatic castration-resistant prostate cancer (mCRPC). *In vitro,* CFON 18801 showed a DC_{50} in the single-digit nM range, and completely arrested the cell cycle in S-Phase by full target degradation within 254 hours, inducing strong immunogenic cell death. CFONs allow a drug-to-antibody ratio from 2-8. Conjugation of CFON 18801 to an prostate cancer-specific antibody showed picomolar cytotoxic activity outperforming a doxorubicin-based conjugate. Its *in vivo* efficacy is currently being assessed.

Justyna Mysliwy, Senior Director of Research at Iksuda Therapeutics Ltd in Newcastle's Biosphere Life Science Ecosystem, presented the company's intratumourally activated ADCs. Not long ago, the first HER2-positive breast, lung and gastric

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cancer patient was enrolled in a dose-escalation study of Iksuda's lead candidate IKS104. The firm's Chinese partner Fosun is already testing the probody ADC in Phase II/III trials, which is cleaved at low pH by the cancer lysosome-selective enzyme beta-glucuronidase, thus avoiding the risk of on-target, off-site toxicity. The probody carries two PDB payloads per molecule.

Conjugation impact

A novel conjugation approach was presented by David Spycher, CSO of Zürich-based Araris Biotech AG. Using microbial transglutaminase, Araris was able to link short, positively charged lysine-containing peptides to HER2-targeting antibodies at their residue glutamine 295 (Q295) without the need for any protein engineering and at a stochiometric drug-to-antibody ratio of 2 or 4. When α-amanitin was used as a toxic payload, complete and long-lasting tumour remission was achieved together with highly reduced toxicity at all dose levels tested. Quantitative biodistribution studies performed with ^{111}In-radiolabeled conjugates showed high tumour uptake and low accumulation of radioactivity in non-targeted tissues.

After raising €54m in Series A financing, Belgian ADC maker ATB Therapeutics BV now claims its technology has solved bioconjugation-related problems. The ATBioFarm platform allows for one-step production of ADCs in tobacco plants. They consist of a targeting antibody, a cleavable but stable peptidic linker and a cell-killing enzymatic payload, and are made by just transferring the encoding DNA sequence into a tobacco-compatible vector that is expressed within the plant cells. According to the technology's inventor COO Max Houry, the ADC-like fusion proteins circumvent common problems of bacterial and mammalian expression systems that occur in the process of attaching toxic payloads in a defined stochiometry to the targeting antibody. Additionally, in contrast to typical payloads, ATbodies use enzymatic cell-killing mechanisms that are complementary to the mode of action of chemotherapeutics

Andreas Bosshard from Molecular Partners AG explained ways of reducing the renal toxicity of radio-Darpin conjugates derived from ankyrin-repeat proteins. To minimise accumulation of radioisotopes in the renal glomerulus, Darpins were produced in which positive surface charges were partly or fully exchanged with negative ones. Although radio-Darpins with fully exchanged charges were significantly less toxic, they were also less effective in reaching the tumour.

Bispecific ADCs also show increased tumour selectivity. Last December, Bristol Myers Squibb licenced global, ex-China rights for the Phase III first-in-class bispecific (EGFRxHER3) ADC izalontamab brengitecan (BL-B01D1) from Chinese SystImmune Co. Ltd for US$800m up-front plus US$500m near-term payments in a US$8.4bn biobucks deal. As the toxic camptothecin payload (DAR 7.5-8) still belongs to the classical payload trio – supertoxic anti-mitotics, DNA alkylating agents and dominating topoisomerase 1 inhibitors (53%) – the recommended dose in humans is still low (2.5mg/kg, preclinically 10 mg/kg) and miles away from what is regarded as optimal for good biodistribution (6-10 mg/kg, see interview p. 40). However, the reported objective response rate was 60% in Phase I/II, with neutropenia as the most reported adverse effect (ADE).

A new approach?

A discovery by scientists at the University of Pittsburgh and the UPMC Hillman Cancer Center is kindling hopes of ending the stealth strategies of solid tumours that put immune cell therapeutics to sleep in the TME once and for all. The team discovered that lactic acid pumped out of the tumour appears to contribute significantly to so-called T-cell exhaustion. At the same time, they discovered that this lactate sensitivity disappears when they blocked the T-cell lactate transporter MCT11 with antibodies (Nature Immunology, doi: 10.1038/s41590-024-01999-3). The antibody, which significantly improved the control of tumour growth in mice, is now to be tested clinically. "Blocking access to inhibitory metabolites is a completely new approach to how we can reactivate the immune system," said lead author Greg Delgoffe, Director of the Tumour Microenvironment Center at UPMC Hillman. "If we get rid of MCT11, there is no difference in the expression of co-inhibitory receptors on T cells," Delgoffe added. "MCT11 is an attractive therapeutic target because it is almost exclusively expressed by exhausted T cells that concentrate in tumours. This makes it a potentially more selective and targeted treatment option compared to other immunotherapies, such as PD1 checkpoint blockers." Bispecific (PD1 x MCT11) Innate engagers could therefore be a future option in the ongoing fight against cancer. ■

The next PEGS Europe will be held on 11-13 Nov. 2025 in the Lisbon Congress Center

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New antibody formats need custom research

PEGS EUROPE Biotech CSOs, CDMOs, CROs, lab specialists and AI developers gave an in-depth insight into next-generation protein-based therapies to about 1,500 attendees at the 16th PEGS Europe in Barcelona. Several new formats are expected to enter the market in the next few years that might significantly reduce the side effects of CAR-Ts, bispecific antibodies, ADCs, and improve their efficacy. As the innovators are SMEs or virtual companies, they depend on support with tools and services.

At US$230.87bn, monoclonal antibody therapies accounted for the majority of the US$416.65bn global market for biologics and biosimilars at the end of 2023. However, at the 16th PEGS Europe in Barcelona, drug hunters from a new Venture Capitalist that has already raised US$1bn told European Biotechnology that "the golden age of antibodies is still to come". New formats such as bispecific antibodies, antibody drug conjugates (ADCs), multispecific T-cell engagers activated in their target tissue to prevent off-target toxicities as well as further engineered modalities such as bispecific 4th and 5th generation CAR-Ts, TCR-Ts and protein degraders presented by biotech start-ups at PEGS Europe are not only emerging from the development pipelines but also from partnerships with tool, service and AI providers (see p. 39).

For instance, British Nuclera Ltd announced a partnership with French CRO Domainex – the first of its kind – that is going to use its eDiscovery platform for custom protein production. Though Yumab CSO André Frenzel told European Biotechnology that developers have become careful in selecting AI partners, they announced a partnership with Japan's MOLCURE Inc to use the AI specialist's platform for *in silico de novo* design of antibody sequences based on antigen sequences and/or target structures.

About 150 sponsors and exhibitors presented their results, products and services at the 16th PEGS Europe 2024 in Barcelona.

Picture: © BIOCOM

Many presentations at PEGS Europe demonstrated that the approval of newly engineered bispecific antibodies, ADCs, and CAR-T cell therapies has picked up immensely since 2021. "To date, 13 ADCs and 17 bispecific antibodies have been approved, representing global sales of US$10bn and US$8bn, respectively," said protein engineering expert Dr Christian Klein, who recently moved from Roche to early-stage investor Curie.Bio (see short interview). "ADCs and bispecifics are the fastest growing class of therapeutic antibodies. This is also reflected in the current deal activity."

Growing with new markets

As targeting, toxicity and affinity challenges have to be overcome, drug developers were seeking for the next-gen solutions at the PEGS Europe exhibition, particularly in the fastest moving field of bispecific antibodies. With nine marketing authorisations from 2021 to 2023

alone, bispecifics are a particularly attractive antibody format, not least because of their potential to demonstrate completely novel mechanisms of action for the treatment of various diseases that cannot be achieved with monospecific antibodies. The antibodies presented at PEGS included tumour-eliminating T-cell engagers with reduced toxicity, which was achieved by switching target affinity, NK-cell engagers, and macrophage cell engagers. Furthermore, dual-targeted specific ADCs with selectivity for defined cancer types were presented, along with the cis-targeting of T-cell subsets using dual checkpoint inhibitors or cytokines. Further developments invvolved degraders of cell surface proteins, formats that pass the blood-brain barrier and those that can switch bsAbs on/off in the tumour microenvironment to prevent undesired peripheral toxicities, cytokine and coagulation factor mimetics, and many more (see p. 12). Specialised service providers and sponsors also presented novel methods such as single-cell sequencing, proteomics, cryo-EM, machine learning, and AI and ML solutions that promise to overcome development challenges such as a narrow therapeutic index, premature protein aggregation, unselective release of toxic payloads of ADCs and radiopharmaceuticals, biomanufacturing issues and a lack of selectivity for target sites.

In lectures, exhibitors presented innovations including microfluidic technologies (Lightcast, Sphere Fluidics), tag technologies to scale and automate protein production/expression (IBA Biologics, Absolute Biotech, BioRAD), high-throughput screening of tumour-selective T-cell engagers and other antibody formats through combination of machine learning and cell-based functional assays (LabGenius plc, Genscript Inc., Biointron, Cradle), and ML-driven screening of antibodies for difficult targets (Yumab, Ailux Biologics, PipeBio, BioMap). Other technologies or services covered included *in vitro* antibody libraries (Specifica/an IQVIA company), protein expression/contract manufacturing (Fuji, Asymbio, GTP Bioways, Excellgene, ThermoFisher), and preclinical modelling (GemPharmatech, Bioneer, The Jackson Laboratory).

Successful exhibition

"Participants discussed all aspects of protein and antibody engineering with expanded coverage of AI/ML, drug targets, multi-specific antibodies, immunotherapy, analytical characterisation and developability, protein expression, oncology, and much more," the conference organisers of the 16th Annual PEGS Europe Summit from Cambridge Healthtech Institute told European Biotechnology Magazine. In the end, the CHI management was pleased with "nearly 1,500 attendees from 38 countries, including 300 speakers and more than 150 sponsoring companies from industry." ■

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Getting started effecively

Getting seed and Series A financing while minimising long-term dilution, but getting all essential functions of a large biotech company – how does that sound? At PEGS Europe, European Biotechnology spoke with Nina Kreymborg, SVP, CSO Partner Team at the VC specialist Curie.Bio.

EuroBiotech_What is unique about what Curie offers?

Kreymborg_Curie.Bio is designed to improve founders' probability of success in creating impactful medicines while also helping them maintain ownership in their company. We invest and leverage our large team of experienced drug hunters and biotech operators to help founders design and execute optimal research and operational plans. We co-pilot alongside the founders and provide proprietary access to world-class experts, external vendors, and future investors. We help founders to create not only scientifically exciting but also financially profitable and operationally sound companies to succeed in their journey of turning their ideas into actual medicines.

EuroBiotech_What is your typical investment and which companies do you support?

Kreymborg_We invest around US$7-12m into each therapeutics start-up. We must be excited by their science and believe they can deliver a drug that competitively addresses a major unmet medical need. We are agnostic to therapeutic modalites and indications and give support to companies across various geographies.

EuroBiotech_Why did you join Curie.Bio?

Kreymborg_I am excited to be part of Curie.Bio because of the value Curie sees in exciting science, because of the emphasis Curie puts on reliable and trustworthy interactions with founders and partners, and because of the outstanding team of professionals. "It takes a village to raise a child" and a team of experienced, creative, knowledgeable, and truly collaborative experts to develop a drug or build a company. That team is Curie.Bio. ■

Picture: © Curie.Bio

Getting to the next stage in ADC development

ANTIBODY DRUG CONJUGATES Toxicity problems due to unstable linkers limit the therapeutic index of Antibody-Drug Conjugates (ADCs). Shortly before the PEGS Europe summit, Chinese BigHat and Lonza subsidiary Synaffix BV signed an agreement for the production of ADCs using machine learning (ML). Here is the background.

Machine Learning (ML) was a hot topic at PEGS Europe Summit, organised by CHI, with many AI/ML companies exhibiting and reporting how their latest algorithms could help bioengineers to optimise their antibodies and constructs. "Optimisation with the help of AI is years away because we don't have enough clinical data to feed AIs for antibody or even ADC development," experts told European Biotechnology at the must-attend meeting for European protein engineers. "It makes no sense to take preclinical data and feed them to an algorithm", another said, "because in vitro is so poorly predictive for in vivo and preclinical in vivo is so poorly predictive for clinical in vivo." However, experts agreed that AI can help in rational design. Financings, such as that of Dutch-Swiss ML startup Cradle NV, which announced a €69.5m Series B financing led by IVP and existing investors after the Summit, documented a high interest to integrate AI/ML in development or QS processes. A number of either antibody or ADC developers no longer want to sleep through the development and thus have set up partnerships.

Partnering with algorithms

One expample is German antibody development CRO Yumab GmbH, which seeks synergies with Japanese ML start-up Molcure Inc. Another one was announced right before PEGS Europe by ADC specialist Synaffix BV. Synaffix' collaboration with Chinese BigHat Bioscience Co. Ltd was the first after Lonza Group took over the Belgian company this May for €100m upfront + €60m in milestones. It combines Lonza Group's end-to-end ADC development and manufacturing platform with Synaffix's clinical-stage platform technology for the development of antibody-drug conjugates (ADCs) with best-in-class therapeutic index. Because Lonza as a huge CDMO was interested in Synaffix' know-how, aka its people, but not its huge proprietary and partnered (around US$10bn biobucks)

pipeline, the Belgians spun off three proprietary ADC assets into the start-up KIVU Bioscience Inc, which closed a US$92m Series A financing led by Novo Holdings at the end of October. Insiders told European Biotechnology, Synaffix' deal with BigHat Bioscience was only possible because the Chinese were attracted by both; Lonza's expertise in contract manufacturing under a single quality system encompassing all critical development and manufacturing activities, including the production of the antibody, bioconjugation, and drug product filling plus Synaffix' GlycoConnect™, HydraSpace® and toxSYN® ADC technologies.

According to the agreement, BigHat will combine Synaffix technology with its proprietary ML antibody design platform for the development of a new ADC programme which is at IND-enabling stage and is on track to be BigHat's first clinical stage programme. BigHat's AI/ML-powered antibody design platform, Milliner™, integrates a synthetic biology-based high-speed wet lab with state-of-the-art ML technologies into a full-stack antibody discovery and engineering platform, to engineer antibodies with more complex functions and better biophysical properties.

What ML can improve?

BioHat's approach – similar to that of Cradle, UK-based Labgenius and other players that seek to combine wet-lab data, automation and ML/AI to find candidates with optimised attributes – promise to reduce the time for candidate discovery and validation in a sector where time to patent expiry is cash. However, as mentioned in some PEGS lectures and round tables, wet lab data sometimes only comprise 700 to 800 datapoints per screening cycle, which might be not enough for algorithms to learn from.

BigHat's next-gen ADC candidate was optimised on its Milliner platform for maximum payload delivery to tumour cells (= linker stability) and optimal drug-like properties. The incorporation of Synaffix's ADC technologies aims to further improve the safety and efficacy of BigHat's next-generation ADCs by making them more durable, with greater on-target toxicity and, consequently, a larger therapeutic index—similar to the preclinical ADC trio spun out into KIVU Bioscience.

Hype towards ADCs

Lectures on ADCs were a major focus at PEGS Europe. According to Floris van Delft, former CSO of Synaffix and now Head of Research at Lonza, the transition rate of ADCs is above 15% in oncology, while antibodies and small molecule drugs had a success rate of 10% and 5%, respectively. That is probably the reason why so many companies at PEGS Europe go for ADCs. According to Chinese scientists who published a global database called ADCdb last year, there were 6,572 projects ongoing, 346 of which were clinical. However, most of them suffer from a low therapeutic index, they simply show too much off-target toxicity due to systemic release before reaching their target(s).

Early-generation ADCs from Daiichi and others experienced significant release of linker-payload outside the tumour, resulting in less pronounced on-target toxicity, while off-target toxicity became the dose-limiting factor. At PEGS Europe, it became clear that the challenge for the sector currently is to add stability to linkers and enhance tumour selectivity and on-target toxicity with less toxic new payloads, as reported by several companies (see p. 14) in Barcelona.

New generation of payloads

Experts told European Biotechnology what's needed to write ADC success stories: "We need a new generation of payloads for ADCs that are less potent than PBDs and have a lower drug-to-antibody ratio (DAR) to reduce toxicity or broaden the therapeutic index. For tubulin inhibitors such as MMEA, a DAR of 4 limits the maximum tolerated dose to 1.8-2.2 mg/kg. However, for good biodistribution, a higher dose is better." Good biodistribution means a MTD as high as 5 to 10mg/kg, according to pharmacologists. Thus, the current credo is: if the DAR goes down, the dose can go up. Many current clinical or approved ADCs could be dosed up to 3 mg/kg but have a DAR of 8. ■

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Global CDMO Lonza AG announced to build a new bioconjugation production site with 800 m² of manufacturing space at Lonza's Ibex® Biopark in Visp, in October.

Pictures: BioAlps Association/Lonza