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Interview

Olivier Litzka from Andera Partners on VC and how the biotech industry is working its way out of the trenches.

Targeted radiotherapy powered by Biotech

Clinical studies: CTIS
The new EU study portal is well-meant, but disappointing

CRISPR/Cas & Co.
Europe set to fail at setting up liberal rules for new breeds

Bioprocessing
Industry growth is hampered by a lack of qualified personnel

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Cultivated meat debate clouded by misinformation

SETH ROBERTS, is a policy manager with the international nonprofit and think tank the Good Food Institute Europe, specialising in the regulation of food such as cultivated meat and precision fermentation. He has expertise in EU and national government food safety policy and works with public authorities, food safety experts and businesses to secure a clear and evidence-based regulatory path to market for alternative proteins. He brings experience from the UK Civil Service and the House of Commons.

As cultivated meat moves closer to commercialisation, we are seeing a worrying trend of misinformation entering the public debate. This food can play a vital role in ensuring Europe's food system is fit for the future – helping satisfy the growing demand for meat while boosting food security – but political opposition has mounted, with the Italian government taking the controversial step of banning cultivated meat.

Many of the false claims dominating the debate leading to this ban were repeated in an item of 'any other business' brought to a recent meeting of the EU's 27 agriculture ministers. This included references to a preprint UC Davis study claiming cultivated meat would have a larger carbon footprint than beef – highlighted by a Changing Markets Foundation report as having been used as part of a misinformation campaign.

As well as not being peer-reviewed, this study is based on the incorrect assumption that the commercial production of cultivated meat would rely on pharmaceutical-grade cell culture media. This doesn't reflect current practices, and peer-reviewed data has shown that food-grade ingredients can support cell growth. The findings deviate significantly from the wider literature, including a peer-reviewed study, based on input from cultivated meat companies and media suppliers, showing that producing cultivated meat at scale using renewable energy could lower climate emissions by 92% compared with conventional beef. The note also cited a 2019 University of Oxford study as evidence of cultivated meat having worse climate impacts than conventional meat. In fact, while this study was conducted when cultivated meat research was less developed and was based on a fossil fuel-intensive energy mix, it still found that cultivated meat is much better for our climate than the 'best' conventional meat production systems for at least the next 100 years.

Another claim is that cultivated meat does not provide higher animal welfare standards due to the use of foetal bovine serum (FBS). But while FBS is used as a medium in biotechnology settings, its price, inconsistency and limited supply means it cannot be used for producing cultivated meat at scale. Many companies have moved away from it and an FBS-free cultivated meat product has been approved in Singapore. It's vital that these debates are informed by evidence and aren't clouded by misinformation. For those looking for it, there is a wealth of independent information such as FAO & WHO and UNEP reports providing details about cultivated meat's safety profile and environmental benefits.

The field has moved on a lot since it was developed by Dutch scientist Dr Mark Post just over a decade ago but remains in its infancy. The EU is home to some of the world's best scientists in this area, but they need certainty from policymakers if their innovations are to benefit Europe rather than being used overseas. ■

COVER STORY

Targeting cancer with Radio-Biotech

Radiopharmaceuticals have turned into a hot commodity when it comes to M&A financing and deals. Targeted therapies that employ high-energy attachments linked to antibodies, small molecules or peptides promise fewer side effects and a localised attack on the tumour. Novartis initially cracked open the door with an innovation from France. Now investors are trying to play catch-up, and startups have seen a surge in demand. The companies involved are both toolmakers and those digging for radioactive gold.

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CLINICAL STUDIES

Critics on CTIS

Even before its launch last year, drug developers, CROs, ethics committees and clinicians began criticising the technical implementation of the EU study portal CTIS. Though the most serious programming errors have now been eliminated by the EMA, the goal of simplifying the registration of multi-centre trials and making the bloc more attractive to trial sponsors was clearly missed.


54

NGT


6

NGTs: No smart rules?

Although the European Parliament has voted in favour of the EC's draft regulation putting 94% of plants bred using new genomic techniques (NGTs) on an equal footing with conventional plants, EU ministers are unable to come to an agreement. This means that the law is in danger of failing.

SPECIAL

Bioprocessing

Pictures: © MicroHarvest (left); EU/PhilippeStirnweiss (middle); BIOCOM AG (right); BIOCOM; Jardel Bassi - stock.adobe.com

EDITORIAL

Climate alarm

Anyone who has seen the film 'The Day After Tomorrow' won't be thrilled by the climate modelling published recently by Dutch researchers. They predict a drop in temperature of 2°-3° Celsius per decade by the end of this century in the northern hemisphere due to a predicted collapse of the North Atlantic Current (AMOC) as a result of global warming and resulting disruption to how seawater of different salinities mixes. While the northern hemisphere is cooling, says the model, the southern hemisphere will grow hotter and hotter – with presumably devastating weather extremes similar to those in the film.

The scientific alarm is an urgent reminder of the need for action. The time for politically motivated, industry-friendly climate cosmetics must come to an end. This means finally investing massively in climate-friendly biotechnologies, as the US has done with its bioeconomy strategy focussing on the potential of synthetic biology. The still baffled, Brexiteered UK wants to follow suit with the announcement of £2bn over 10 years.

The plans focus on biotech in medicine, food production and the breeding of climate-adapted plant varieties. The EU, on the other hand, is currently failing to adapt the authorisation of new genomic techniques, the acceleration of clinical trials and photosynthetically produced biodiesel. What has to happen to finally force change?

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Thomas Gabrielczyk
Editor-in-Chief

Final spurt around NGT regulation

EU After the European Parliament approved a relaxation of EU genetic engineering rules for plant varieties made by new genomic techniques at the beginning of February, the ball is now in the court of the EU Council of Agriculture Ministers, which narrowly failed to achieve the required qualified majority in two votes – in mid-December and at the beginning of February.

Opponents of CRISPR-Cas and other cis-genic techniques in plant breeding are on the verge of success in the dispute over the deregulation of the strict EU genetic engineering rules for plants bred with new genomic techniques (NGT). Though the novel breeds' species-specific DNA of so-called NGT-1 plants has been genetically modified, it is indistinguishable from plants bred with conventional breeding techniques. For all other cis-genic breeds (NGT-2 crops) mandatory labelling and all other rules of the current GMO rules that regulate transgenic plants apply.

No trilogue possible?

Until mid-February, things looked good for those in favour of deregulating NGT-1 breeding, which they hoped would speed up the EU market approval of climate-adapted crops. In mid-December, the EU Council of Agriculture Ministers failed to reach a qualified majority – although the required 15 votes in favour were achieved, they fell just 7.5% short of the required 65% of the EU population. However, in January, the AGRI and ENVI committees of the European Parliament voted in favour of an amended draft law that provides for mandatory product labelling and a patent ban on NGT-1 and NGT-2 plants (see p.38). At the beginning of February, the European Parliament followed suit with a narrow majority (307 votes to 263, with 41 abstentions). A further vote by the EU agriculture ministers resulted in 16 votes in favour and a majority of just under 60%. According to ENVI committee rapporteur Jessica Polfjärd (EPP, SE), "NGTs are crucial to strengthen Europe's food security and to green our agricultural production. The new rules will allow the development of improved plant varieties that can ensure higher yields, be climate resistant or require fewer fertilisers and pesticides. I hope member states will soon adopt their position so we can adopt the new rules before European elections and give the farmers the tools they need for the green transition."

At the beginning of February, the European Parliament voted in favour of relaxed regulations for NGT plants by a majority of the EPP, Renew group, and socialists.

Pictures: EU - PhilippeStirnweiss

According to Pascal Canfin, Chair of the ENVI committee, it is highly unlikely that the legislation will be approved before the EU elections in June if EU countries do not reach an agreement in "the next few days". EU observers assume that it will no longer be possible to finalise the trialogue by the end of February alone, as the trialogue talks can only begin once the Council of Ministers has given its approval. An agreement by the end of February is necessary in order to be able to adopt the NGT Regulation in the last session of the European Parliament in this legislative period.

The ball is now in the court of the Commission and the Council. NGOs and the Greens are protesting against the regulation, as they believe it jeopardises GMO-free organic farming and restricts consumers' freedom of choice. Lobby organisations Euroseeds and EuropaBio were split on a patent ban (see expert comment, p. 38) for NGT crops. While Euroseeds Petra Jorasch advocated for an IP system that balances effective protection and fair, broad access, EuropaBio warned to establish sector-specific IP rules. ■

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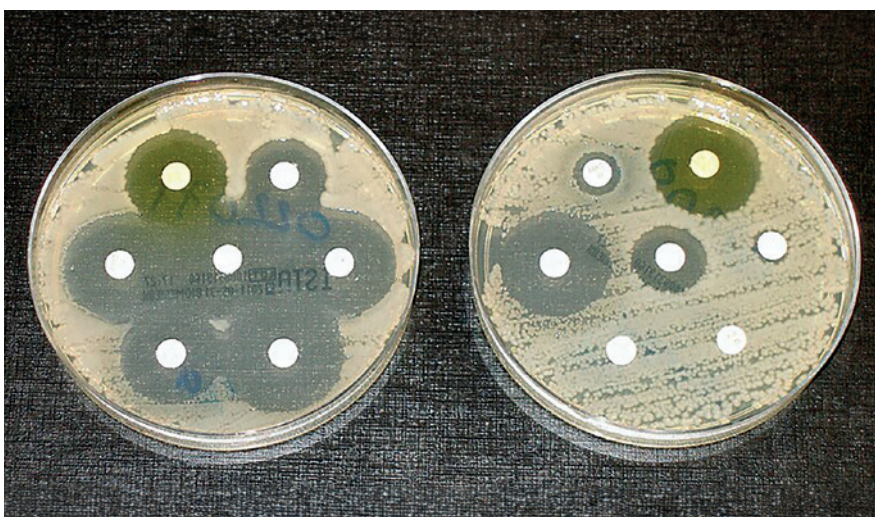
Antimicrobial resistance: money alone is useless

AMR While the Novo Nordisk Foundation is investing around US$25m in early antibiotic development of SMEs funded by CARB-X, the planned introduction of transferable exclusivity vouchers as part of the General Pharma Legislation is still pending due to delays in the legislative process. That's bad news for academic spin-outs developing new antimicrobials.

Members of the European Parliament believe that the European Commission's ambitious legislative package on General Pharmaceutical Legislation (GLP) will not be passed before the European elections and the new EU Commission take office. It provided for so-called transferable exclusivity vouchers (see EUROPEAN BIOTECHNOLOGY 2/2023) as an incentive to develop new antimicrobials fighting priority pathogens, which are primarily developed by biotech SMEs. This puts the financing of promising AMR drug candidates in Europe on a shaky footing.

However, there was a drop in the ocean at the beginning of January. The Novo Nordisk Foundation has committied up to US$25m to support the early-stage development of drugs, vaccines and diagnostics to prevent, diagnose and treat priority microbial pathogens from the CDC and WHO list of infectious threats. The Danish Foundation is granting the investment to the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) over three years. The Foundation joins four G7 government departments or agencies, the British Wellcome Trust and the Bill & Melinda Gates Foundation in supporting CARB-X.

CARB-X supports product developers within academic spin-outs and small companies in need of grants and guidance. The partnership, therefore, plays a crucial role in moving promising ideas for cutting-edge antibacterial products from basic research to clinical development and through Phase I trials. Since 2016, CARB-X has funded 93 projects in 12 countries. Nineteen projects have advanced into or completed clinical trials; 12 remain active in clinical development, including late-stage clinical trials; and two diagnostic products have reached the market.



Antibiotics sensivity testing. The bacteria on the right plate seem to be less sensitive to antibiotics than those on the left one.

Picture: © Dr Graham Beards - wikipedia.org

Huge need for progress

According to the World Health Organization, "the clinical pipeline and the recently approved antibacterial agents are insufficient to tackle the challenge of increasing emergence and the spread of AMR." Private investments in innovative antibiotics are poor partly because doctors use them only when older and cheaper drugs fail. This is important to prolong their effectiveness, but it also limits their sales. Due to the strategic stepback of pharma companies from the risky early development of new antibotics, there is a huge funding gap in antibacterial product development. According to estimates of the European Commission, between US$250m and US$400m must be invested annually by public and philanthropic sources to fill the development gap.

Novo Holdings established the REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund in 2018 to address this early-stage funding gap. While continuing to support the existing portfolio, REPAIR has paused new investments due to the challenging market conditions, with the Foundation now supporting the critical early-stage pipeline via the philanthropic grant to CARB-X. The organisations are engaged in a range of activities from early development to advocating for payment models that can help rejuvenate the market for antimicrobials.■

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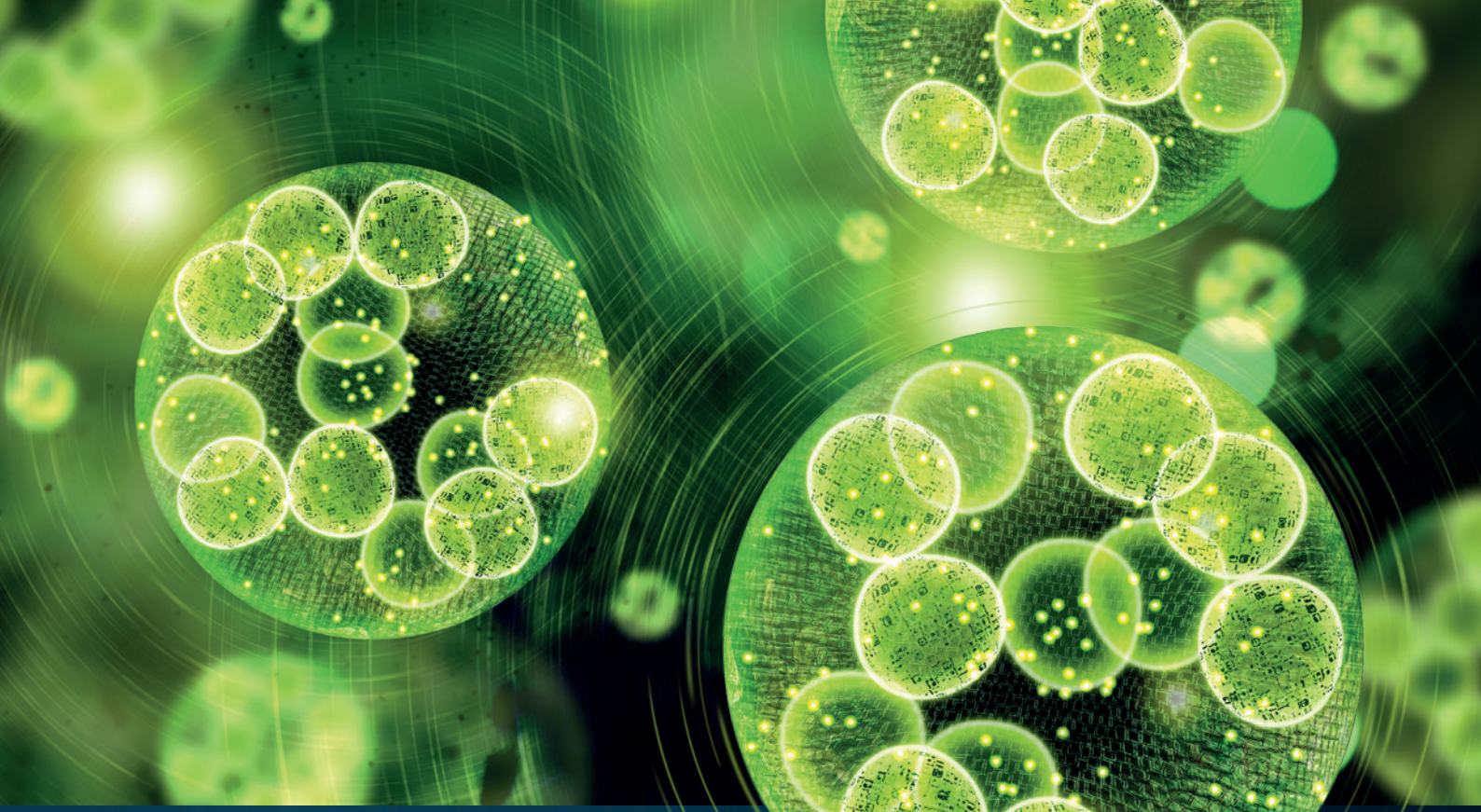

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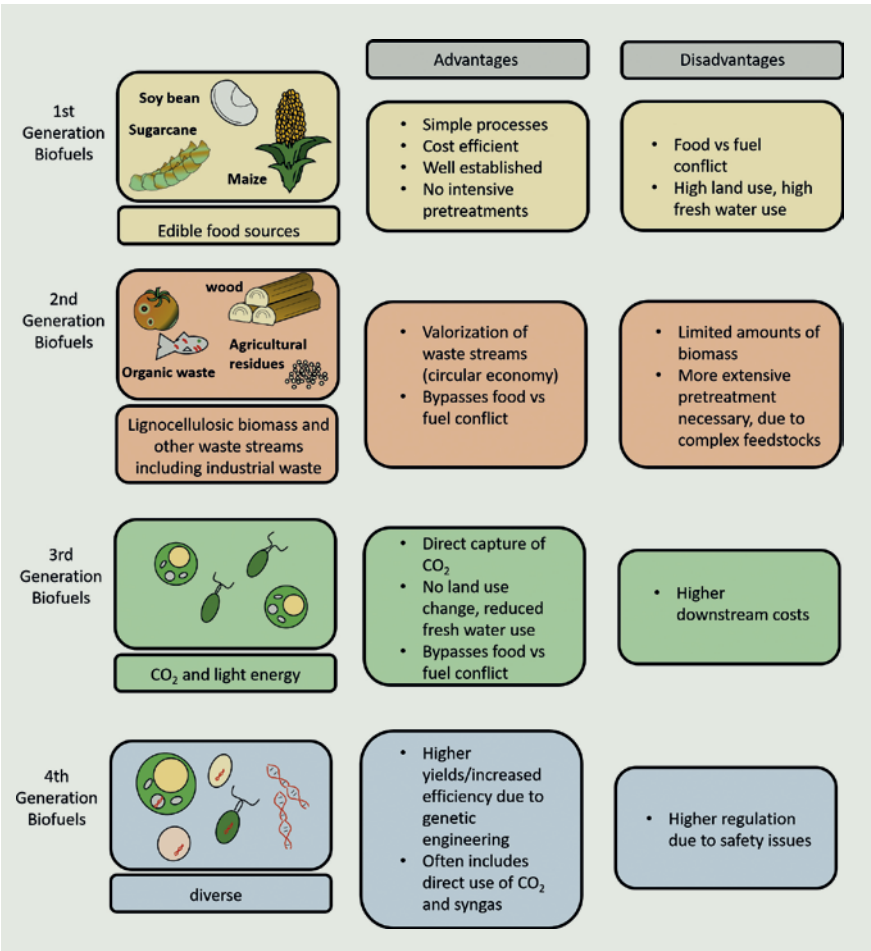
Heavy-duty car emission reduction: chance for biofuels

TRANSPORT As the transport sector accounts for 17% of global CO_2 emissions, MEPs last year confirmed the 90% reduction target by 2040 compared to 2019 levels, proposed by the EU Commission for new heavy duty vehicles. In mid-February, Germany enforced an important exception of the ban of fuel-driven combustion engines. According to the vote in the EU Council, vehicles that run on carbon-neutral fuels may nevertheless be authorised after 2040.

In the postponed vote in the February EU Council of Transport Ministers, Germany took advantage of its position as a populous country (18.72% of the EU population). This is because, in addition to 15 votes in favour from the member states, these must also represent 65% of the EU population in order to achieve the necessary qualified majority. An abstention of Germany would have blocked the majority. Contrary to the Commission's proposal, Germany's liberal-democratic Transport Minister Volker Wissing made his approval dependent on the fact that not only hydrogen, fuel cells or electricity would be permitted as future fuels for heavy duty vehicles, but also CO_2-neutral fuels where tailpipe emissions – which are the data point that matters to Brussels – don't change.

The text of the Commission's amended Regulation adopted by the ENVI committee of the European Parliament after the Council vote contains a new recital that is not legally binding. Specifically, a passage has been inserted that obliges the new EU Commission to examine by 2027 how heavy-duty commercial vehicles that run on climate-neutral fuels such as synthetic or biofuels can be approved and whether these fuels can be taken into account via a "carbon correction factor" in order to comply with the CO_2 fleet limits.



Pro and cons of synthetic biofuels

New hope for fuel producers

Although Wissing's commitment to climate-neutral fuels seems strongly focused on so-called e-fuels, the new text also allows the approval of other climate-neutral fuels such as the advanced production of biodiesel from undemanding marine algae. "We are creating legal certainty for both the manufacturers of commercial vehicles and the manufacturers of climate-neutral fuels," said Wissing after the vote. "At the same time, we are sending a clear signal to the market that we need synthetic fuels. We must keep all technological options open on the way to achieving our climate targets," he added.

Pictures: pbio.3002063.g001

For sustainable production of synfuels, atmospheric CO_2 and hydrogen gas (H_2) produced from renewable energy are processed into combustion fuels in large-scale plants that do not yet exist EU-wide.

Synfuels vs biofuels

The new exception allows for two synfuel scenarios:

- Firstly, the option of refueling trucks, buses, tractors and vans with CO_2-neutral fuels, i.e. using green rather than grey hydrogen or gasified residual biomass.
- Secondly, if 98% of the hydrogen is produced from fossil natural gas by steam reformation, as is the case today, the environment will continue to be polluted.

However, since the electrolysis step in the production of e-fuels results in energy losses of at least 80%, they are at a clear disadvantage compared to electric drives, which have >90% efficiency.

Second chance for biofuels

A more sustainable alternative to e-fuels or biomass-consuming synthetic fuels may be modern biofuels such as algae biodiesel produced from photosynthetic microalgae with a negative CO_2 balance – i.e. 3rd and 4th generation biofuel (see figure p. 10). Most of the 43 EU biodiesel producers organised in the European Biodiesel Board (EBB), which represent 70% of the market, still rely on biogenic materials to produce biofuels not photosynthesis and synthetic biology. However, as 3rd and 4thbiofuels can be produced cost-effectively with saltwater algae in sunny regions and have a high photosynthetic efficiency, they have the potential to bring back combustion machines to the road while emitting only the carbon dioxide photosynthetically fixed before by the algae to build up biomass. In February, British-Malaysian marine algae biofuel start-up HutanBio Ltd has secured an £2.25m seed investment to produce carbon-negative biodiesel in brackish water. ■

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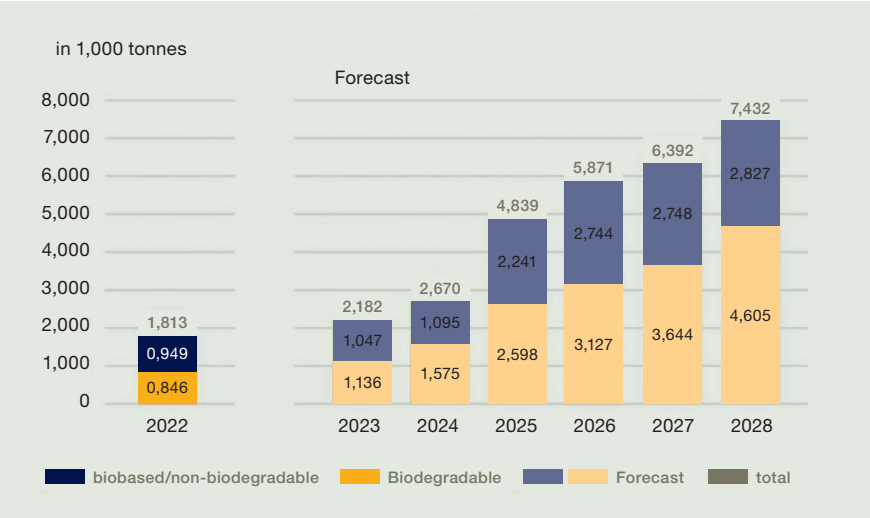
Bioplastics on the rise



Global production capacities of bioplastics

STATISTICS Bioplastics production capacity is set to quadruple by 2028, according to new figures published by the industry association European Bioplastics in mid-February. The study conducted by German nova-Institut GmbH suggest a sharp increase in the production of sustainable plastics in the next two years and calls for policy support.

According to the market study, the global production volume will increase from the current level of around 2.2 million tonnes per year to almost 7.5 million tonnes per year.

"The expansion will be driven by the increasing demand for green material", said Hasso von Pogrell, Managing Director of the industry interest group. Technical developments in the field of biopolymers such as PLA, PHA (polyhydroxyalkanoates) and polyamides are also making rapid progress. The proportion of biodegradable plastics in the total volume of bioplastics will increase from the current 52% to 62% in 2028. For PHA, an increase from 4.8% to 13.5% is expected for the same period.

At the end of January, the association had published a Policy Manifesto, calling on the future European Commission and EU Member States to develop a comprehensive Biopolymers Industrial Action Plan to accelerate the growth of the bioplastics industry. EUBP recommends to harmonise regulations to create a fair level playing field for bioplastics incentivising access to sustainable biomass, increase funding for scaling up bioplastics production, and to close infrastructure gaps to create better access to food waste

"Bioplastics have the potential to play a significant role in reducing the environmental impact of plastics", emphasised von Pogrell. "However, the industry needs a clear and supportive policy framework to reach its full potential." The Manifesto is supported by a wide range of stakeholders, including bioplastics producers, converters, and end-users.

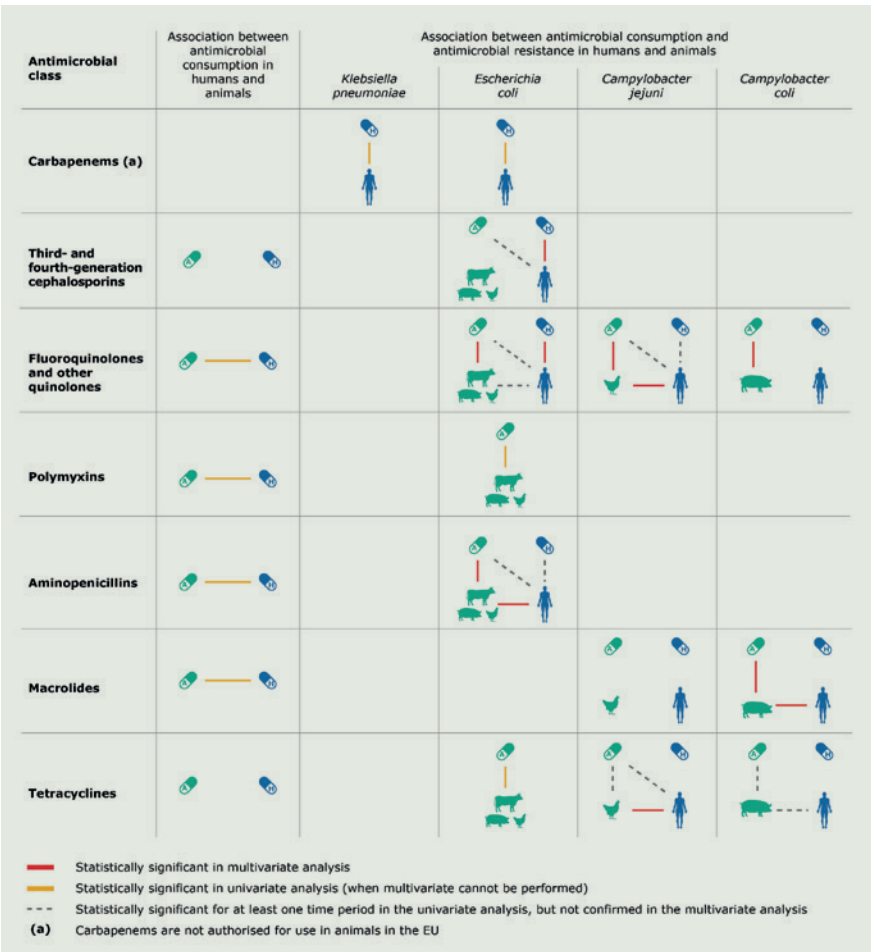
In mid February, German Green Elephant Biotech GmbH was the first company worldwide to launch a plant-based 96-well microtitre plate (MTP) on the market. The MTP is moulded from polylactic acid (PLA). Although the disposal of PLA sheets also produces the greenhouse gas CO_2, the emissions correspond to what the maize plants originally absorbed from the atmosphere. According to the company, the life cycle of its 96-well plates therefore produces half the CO_2 emissions of conventional polystyrene plates. ■

Pictures: European Bioplastics/nova-Institute GmbH

Antibiotics: report urges further reduction

AMR A new report clearly shows that countries that have decreased their consumption of antibiotics in, both animals and humans, have seen a reduction in antibiotic-resistant bacteria. However, the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), and the European Medicines Agency (EMA) call for further reduction.

A new report clearly shows that the 10 of 20 countries that have significantly decreased their consumption of antibiotics in, both animals and humans, have seen a reduction in antibiotic-resistant bacteria. However, the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA), and the European Medicines Agency (EMA) call for further reduction.



Links identified in the analysis between antimicrobial consumption in humans and foodproducing animals and antimicrobial resistance in bacteria from humans and food-producing animals

The 4th JIACRA report presents data collected between 2019 and 2021 on antibiotic consumption and AMR in humans and animals in Europe. For the first time, the three agencies analysed trends of antimicrobial consumption and AMR in the indicator gut bacterium *Escherichia coli (E. coli)* from both humans and food-producing animals. From 2014 to 2021, antibiotic consumption in food-producing animals decreased by 44% which in turn could reduce antibiotic resistance.

Measures taken work

ECDC Director Andrea Ammon concluded that "using fewer antibiotics in livestock production pays off: in most countries that reduced antibiotic use, we observed a corresponding decrease in resistance levels." EFSA chief Bernhard Url underlined that access to reliable data on consumption and resistance in people and animals are crucial to identify what measures work. According to EMA head Emer Cooke, the consumption of 3rd- and 4th-generation cephalosporins, and quinolones, is associated with resistance to these antibiotics in *E. coli*. This is also true in cattle farming for quinolones, polymyxins, aminopenicillins and tetracyclines used. The agencies call for further reduction of antibiotic consumption in the 29 EU/EEA countries (humans: 125.0 mg per kg of biomass, food-producing animals 92.6 mg per kg of biomass). ■

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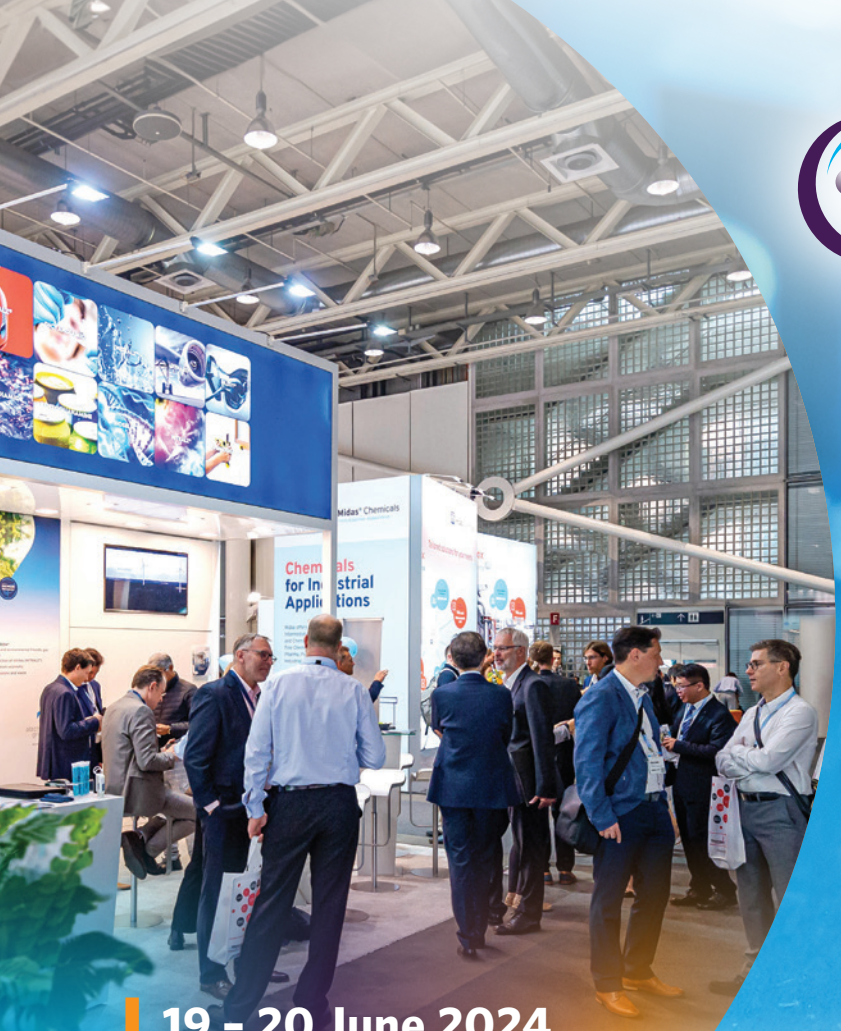

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ONCOLOGY Steel, rays, poison ... those are the traditional medical approaches to treating cancer. Surgery, radiology and chemotherapy – or a combination thereof – have been the weapons of choice for oncologists for decades. Targeted radiotherapy is a newer molecular variant designed to maximise damage to the tumour and minimise damage to surrounding tissue. Now the success of approved radiopharmaceuticals has caught the attention of investors and Big Pharma.

The big idea behind radiopharmaceuticals is to combine the strengths of two kinds of cancer treatments – radiology and targeted therapies. In simple terms, it involves attaching radioactive isotopes to a molecule, then irradiating cancer cells with a high degree of specificity and selectivity by matching those molecules to known targets.

Funding is piling up

Headlines about deals in the pharma industry make it clear that global interest in radiopharmaceuticals is growing, and some major deals in the area stand out. The value of the global radiopharmaceutical industry was estimated at around US$5bn in 2017, and could grow to US$15bn in the coming years in the United States alone, according to industry experts.

Investments in the sector are correspondingly large. Novartis AG alone has spent around US$6bn on acquisitions, and is currently regarded as the global leader in the field. The Swiss multinational entered it in 2017/2018 with its US$3.9bn purchase of French company Advanced Accelerator Applications SA and its then-hopeful Lutathera, which addresses gastroenteropancreatic neuroendocrine tumours (GEP-NETs). With its approval in 2018, Lutathera became a major role model in the radio space, and has since been viewed as a door-opener. Later in 2018 Novartis spent a further US$2.1bn to acquire Endocyte Inc., integrating Pluvicto (177Lu-PSMA-617), which uses lutetium (^{177}Lu) – a beta-emitter targeting prostate-specific membrane antigen (PSMA). It received approval in 2022.

Although the pandemic posed major challenges, more deals followed soon. In June 2021, Bayer AG acquired Noria Therapeutics Inc. and PSMA Therapeutics Inc. The aim was to develop a prostate cancer treatment that uses a small molecule to deliver radioactive therapy to cells carrying PSMA markers. However, little has been heard to date about this me-too prostate product. Last year Eli Lilly also acquired Point Biopharma Global for US$ 1.4bn after a small bidding war for the two therapeutic programmes. They target metastatic castration-resistant prostate cancer and also GEP-NETs – other me-toos – but the deal included production facilities as a sweetener.

RayzeBio has also recently made headlines. Founded in California (US) in 2020, the company raised around US$418m in four venture capital rounds before going public on the NASDAQ last September with a gigantic IPO totalling US$311m. Its lead therapeutic candidate uses the same molecule as Novartis' Lutathera to also target GEP-NETs, but swaps out lutetium-177 for actinium-225 – an isotope that emits more destructive alpha particles. It's capable of delivering hundreds of times the energy in a much smaller radius, one only a few cells in depth. Just three months later, in December 2023, Bristol Myers Squibb acquired RayzeBio for US$4.1bn, topping off a massive buying spree. In just a few months in the second half of 2023, BMS spent around US$24bn on business development and acquisitions.

Narrow focus on targets

These examples show that the focus of development was essentially on prostate cancer and special forms of neuroendocrine tumours. Similarly, the target molecules are limited to two main focuses of interest: PSMA and somatostatin receptor 2 (SSTR2), which are overexpressed in GEP-NETs and extensive-stage small-cell lung cancer (ES-SCLC). New targets like Fibroblast Activation Protein (FAP) are also slowly getting some limelight, however, as indicated by an in-licensing deal of two FAP-targeting peptides from German biotech company 3BP with Novartis. 3BP (Berlin) is receiving an initial payment of US$40m, and

may see US$425m in development, regulatory and commercial milestone payments.

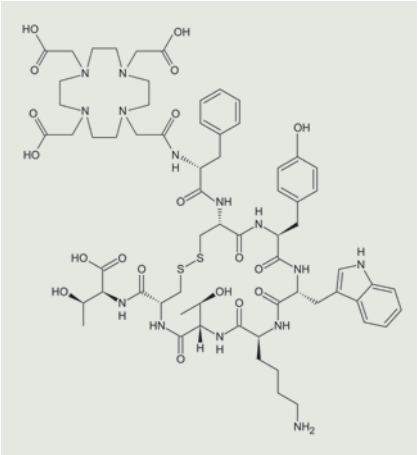
Newcomers ramp up the pace

The action around other startups is also heating up. European-American company ARTBIO (Oslo, London, Basel and Cambridge/US) raised an oversubscribed and scaled-up US$90m Series A financing with investors Third Rock Ventures, F-prime Capital and Omega in December to advance its pipeline and the development of isotope technology for a new class of alpha radiation therapies. In Germany, the newly founded company Ariceum Therapeutics (Berlin) doubled its Series A financing round in spring last year from the end of 2022 to around €48m, with new investors Andera Partners and Earlybird Venture Capital joining existing investors HealthCap, Pureos Bioventures and the billion-dollar fund EQT Life Sciences.

Also in 2023 – and again in the private sector – a substantial financing round totalling around US$250m was publicised for Munich-based company ITM Isotope Technologies. The company, which for research purposes is based near the nuclear power plant at the Technical University of Munich, has continuously raised funds. Little wonder then that the rumour mill has churned out speculation about an imminent IPO. So far, however, one has not materialised, probably due to the lack of a good window.

Production partnerships ...

The field of players in targeted radiotherapy can be broken down into companies that either come from the production of radioisotopes and have mastered the production processes there, those that are suppliers for other radiopharma developers or, like Munich-based ITM, those that have even developed and marketed their own 'isotope generator' for clinical use in imaging anywhere in the world. The global reach of ITM, which has 400 employees, is already quite considerable. Geographically, its activities



A door-opener for radiopharmatherapy was the formal prospective, randomised controlled study of a peptide-isotope chelator developed by Advanced Accelerator Applications SA (France). DOTATATE (DOTATATE,[1] DOTA-octreotate, oxodotreotide, DOTA-(Tyr3)-octreotate,[2] and DOTA-0-Tyr3-Octreotate) is eight amino acids long, with a covalently-bonded DOTA bifunctional chelator.

range from China to Canada and the US, where it was recently granted a manufacturing licence for radioisotopes.

Another company in the segment is Berlin-based Eckert & Ziegler AG, which is very broadly positioned in the radiology product world. It reports a rise in demand for supplies for radiopharmaceutical drug development, alongside many cooperation agreements with international companies. For example, the firm has signed a comprehensive supply contract for therapeutic radioisotopes with Nucleus Radiopharma, a joint venture between the Mayo clinic network (US) and venture capital company Eclipse. Eckert & Ziegler will be the core supplier of high quality lutetium-177 (Lu-177) and actinium-225 (Ac-225), both in non-carrier added form. Eckert & Ziegler will also support the startup ARTBIO in realising the manufacture and supply of its therapies using its proprietary AlphaDirect™ Lead-212 (Pb-212) isolation technology. The partnership aims to accelerate the development of lead-212-based alpha-emitting radioligand therapies, starting with the clinical development of ARTBIO's lead product AB001 for the treatment of – again – prostate cancer. In addition to the US, which the ARTBIO manufacturing process will specifically be developed for, Eckert & Ziegler's global service network for contract manufacturing includes production facilities in Berlin (Germany) and Jintan (China). Competitor ITM also has long-standing manufacturing partnerships in China in place.

Besides the small but growing interest in lead isotopes, supply generally remains focused on lutetium-177 and actinium-225, which are commonly-used radioactive substances in cancer treatment. They respectively emit alpha (Ac-225) and beta (Lu-177) particles to destroy tumour cells. While Lu-177-based drugs have been approved for various indications and are seeing increasing demand worldwide, dozens of clinical trials are underway for both radioisotopes. According to market experts, demand for Ac-225 will increase significantly over the next decade, but a bottleneck at the moment continues to be a lack of GMP quality control. It remains the biggest challenge of all, especially in the academic environment – but more on that in a moment.

... and the hunt for targets

Another group of companies are the gold diggers, and concentrating more on identifying suitable target molecules and selecting the appropriate transporter molecule for the radiating cargo. This field is developing particularly dynamically as VC investors have come sniffing about since the approvals of Pluvicto and Lutathera. Interestingly, startups like these – with an eye for target, active ingredient and linked radioactive isotope – can almost be described as 'next-generation ventures', because they're being built by researchers and developers who were either trained in early successful radiopharmaceutical development projects at large pharma companies, or were involved in early pioneering companies that have since been taken over. Now being poached and hired in new startups because of their experience, they could help bring their expertise to bear in the sector in a more agile

and faster way than they could working for Big Pharma.

In the case of ARTBIO, industry veterans Philippe Dasse and Daniel Rossetto were respectively hired as Chief Technical Officer Head and Senior Vice President of Supply Chain and External Manufacturing at the same time as the Series A deal was finalised. Dasse was most recently Head of Technical Operations for Radioligand Therapies at Novartis Oncology. Prior to that, he was the first employee of Advanced Accelerator Applications back in 2002, and went on to assume increasing responsibility for managing all technical operations until his departure. Rossetto also came from Novartis, where he was most recently Global Head of Supply Chain at the newly-acquired AAA specialty unit. In this role, Rossetto led a diverse team that built a fast and flexible internal and external supply network to deliver the clinical and commercial radioligand therapy (RLT) portfolio, including Pluvicto, to prostate cancer patients.

The German capital calls

Berlin-based Ariceum was able to convince investors like Pureos Bioventures, EQT LifeSciences and Andera Partners by also bringing together a team with relevant experience. CEO Manfred Rüdiger has a track record in several positions at various biotech companies, while Germo Gericke contributes radioligand expertise. Gericke has a long history at Novartis, was involved in the scene from the very beginning, and in part helped to shape it. He speaks of a 'renaissance of radiotherapy', because early projects – when the sector first began finding its feet years ago – were unsuccessful. Even so, he says, they had lessons to teach. "It was only with Pluvicto and Lutathera that the door really opened," Gericke told European Biotechnology. But experts in the field still have a lot to discover. Setbacks can and will occur, and there is still a steep learning curve ahead. After 15 years with Novartis and helping to integrate Endocyte and AAA, Gericke joined Ariceum in 2023.

Ariceum does not see itself as a classic one-trick-pony startup, or as a specialist in one or the other isotope, but rather as a strategic anchor – a strong European radiopharmaceutical company that aims to combine and advance the best approaches with the most effective isotopes, regardless of fixed isotope or target molecule expertise. That's why the newly-founded firm acquired Theragnostics Ltd so quickly after setting up shop itself. Theranostics has its own unique approach to the target molecule and the desired mode of action on the tumour cell. There, an isotope (Auger) is used that emits locally in the nanometer range and is bound to a known PARP inhibitor (DNA repair enzyme). The approach was so convincing for Ariceum's inves-

tors that they simply bought Theranostics and kept on the expert team involved in its design and development.

Both Gericke and Manfred Rüdiger compare the current state of the radiopharmaceuticals field with the course that checkpoint inhibitors took. There, initial successes triggered a wave of imitators, and the ideas for their use and combination expanded enormously in the years that followed. That led to the emergence of today's state of play, which has not only provided new insights into the immune system but also successes in treatment. Both see the gold rush in targeted radiopharmaceuticals in a similar light. Currently, companies that have mastered or have a grip on supply chains in isotope production are being snapped up or financed. At the same time, many firms are still focussing on the known target molecules PSMA or SSTR2, and are trying out new isotopes or light variants of them. On the surface, the spectrum of indications is therefore still very limited. But that's changing as investors grow more willing to take risks, not least because the known field of prostate cancer's target PSMA and GEP-NETS, along with SSTR2, has already been mostly ploughed and cultivated.

Linking diagnostics and therapy

In what are called 'theranostics', a somewhat overused if catchy buzzword, the diagnostic approach is directly combined with the therapeutic application via the same active ingredient molecule. In diagnosis, a small amount of radioactivity is first used to scan a patient with positron emission tomography (PET) – frequently in combination with CT for anatomic allocation – to determine the degree of expression of a target in the tissue. If the attached diagnostic isotope is then swapped out for an emitter that can damage the cancer tissue, the diagnostic molecule can at least theoretically become a radioactive therapeutic agent. .

That's a big 'if', however. The switch from diagnostic to therapeutic agent is not always a slam-dunk. Requirements for diagnostics and therapeutics are not identical. What they have in common is high affinity, specific binding and stability in plasma. But there are also differences in terms of goals. Diagnostics should only remain in the body for a short time, in order to keep a patient's exposure to radiation as low as possible. This can also mean that they only remain a relatively short period of time (a few hours) on the tumour. Therapeutic agents, on the other hand, should remain on/in the tumour for as long as possible (several days for Lu177 & Ac225) in order to be able to develop their effect as intensively as possible during the decrease in intensity determined by their radioisotopic half-life.

In reality, the carrier molecules can be identical (DOTA-TATE with Ga68 and Lu177) or can differ slightly (for instance with Ga68-PSMA-11 and Lu177-PSMA-617). Sometimes, however, the change of isotope from Dx to Tx alters the carrier molecule so much that it has to be 'reinvented' from scratch, a situation that has posed big problems for some companies in the past.

The challenge of toxicity

A diagnostic agent does not have to be as selective as a therapeutic, because the radiation exposure for healthy tissue is lower, while temporary accumulations of the agent in the blood, kidney or liver don't generally pose a problem for the organism. However, the accumu-

Radiolabeling (I) in ITM Isotope Technologies SE facilities. The company is headquartered close to the nuclear power plant at the Technical University of Munich.

Picture: © ITM Isotope Technologies SE

The right emitter of choice

Alpha is the largest particle with the least penetrative power. With a short particle range and high linear energy transfer, alpha-emitting radionuclides demonstrate high cell-killing efficiencies.

Beta-emitting radioisotopes have the longest particle pathlength (≤12 mm) and lowest linear energy transfer (LET) (0.2 keV/µm), supporting their effectiveness in medium to large tumors. Although the long particle range is advantageous in evenly distributing radiation dose in heterogeneous tumors, it can also result in the irradiation of healthy tissue surrounding the tumor site.

Auger electrons have high LET (4–26 keV/µm) but a limited path length of 2–500 nm that restricts their efficacy to single cells, thus requiring the radionuclide to cross the cell membrane and reach the nucleus.. ■

lation of high radiation exposure in the liver or kidneys is a major challenge for radiotherapeutic agents.

This is where the different variants of active-substance molecules come into play. Antibodies have a longer blood half-life, and peptides are retained in the kidneys in order to be recovered in their individual building blocks from amino acids. In this process, the residence time of the radioisotope in these organs and possible collateral damage to these tissues is a balancing act. Exploring organ-specific radiation levels may seem secondary when initially treating a condition like a diseased prostate gland. But the collateral enrichment of radioactivity in the spleen or bone marrow is an issue. So the balancing act doesn't just involve finding a good target molecule on the surface of cancer cells in the solid tumour tissue. Nowadays, every radiopharmaceutical's degradation and excretion pathways must also be taken into account. Each variant cargo molecule has different advantages and disadvantages, and they can be evaluated.

Another topic is specificity. PSMA for example is also expressed and accumulates in the lacrimal and salivary glands, nasal mucosa, liver, spleen, kidneys, intestines and bladder. The choice of the best isotope in terms of benefit-risk assessment therefore has to be taken very seriously, because hitting the prostate tumour hard and repeatedly will also eventually severely damage or destroy those other tissues as well.

Tissue toxicity has therefore stood in the way of the rapid expansion of radiopharmaceutical treatments, and any application has to be proven safe as a top priority.

Grey areas of application

That led the pharmaceutical industry as a whole to initially turn its back on the field, and its potential was mostly further developed in academia. More recently, this has led to a very lightly regulated area of application for radiopharmaceuticals as "compassionate use", a kind of last straw for the cancer patients concerned.

For other classes of therapeutic agents, it would have been unthinkable that, as in the case of Pluvicto, around 2,000 patients had already been treated 'compassionately' with the compound before the start of the first clinical trial. Viewed critically, one could say that those thousands of patients were treated as guinea pigs.

But at least the results were positive, and provided insights into how radiopharmaceuticals can lead to noticeable treatment success in patients. Pluvicto showed an impressive response in the authorisation-relevant study. Still, some industry experts say the lack of regulation has led to a kind of 'Wild West' of drug development in the sector.

Pragmatic regulation needed

Germo Gericke is also critical of the fact that regulation is not keeping pace with developments. He says that compassionate use is undermining a commercial market environment, which in turn unsettles investors and lulls reimbursers from health insurance companies into a false estimate of prices and what development actually costs. Another issue is that whereas drug development is harmonised in Europe with the EMA as a central authority, this is not the case for federal offices for radiation protection. Although calls for more regulation and harmonisation are not exactly typical for the pharma industry, this is an issue in radiation protection, and the fragmentation of rules slows European development. The FDA and even its Chinese counterpart, the CFDA, have on the other hand set pragmatic, scientific regulatory requirements, and these have an effect on innovation.

Industry vs. Academia

Industry experts have yet another concern – the home-brew tradition of some clinicians in providing isotope ligands for imaging or even therapy through special labs located in the pharmacies of some university hospitals. They only cover established markers or targets, and rarely take an innovative turn. But clinicians in academia

Radiolabeling (II): a manipulator in the process cell

don't want to give up established procedures. In the context of the reform of the European Union Pharmaceutical Framework, the manufacturing of nuclear medicinal compounds is under review and will see new regulation. The pharma industry in radioligand diagnostics and therapeutics has serious doubts that home-brewed compounds make a relevant and qualitatively equivalent contribution to patient care and urges that GMP manufacturing must become the standard. The unspeakable argument by some academic associations that patients deserve individualised treatment in this context has to be dispelled.

Radiopharmaceuticals are regulated as drugs and need to be developed and manufactured with the same level of care as other classes of therapeutics (e.g. biologics, small molecules, cell therapies, vaccines). Also, they will only be approved by FDA or EMA based on well-run clinical trials providing a clear understanding of efficacy versus side-effects in well-defined patient populations. With the expansion of radioligand therapy, many questions about both radiobiology and the interaction with the immune system will be answered, and only a clear regulatory framework can help pave the way for better medicine.

With the growing success of radiopharmaceuticals, a broad spectrum of specialized CDMOs is evolving across the world, larger pharma companies will have manufacturing facilities of their own. The homebrew era has to come to an end. ■

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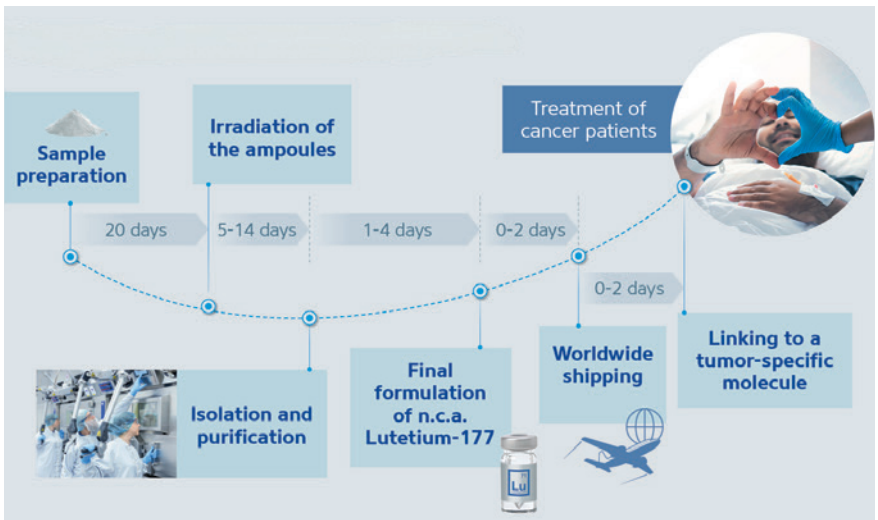
Pictures: © ITM isotope technologies SE

Meeting rising demand

RADIOPHARMACEUTICAL THERAPY Radiopharmaceutical Therapy (RPT) is offering several advantages over existing therapeutic strategies. The highly sought-after therapeutics require a sophisticated supply chain, as radioisotopes have short half-lives and must be delivered to patients with extreme speed and efficiency. ITM rises to this challenge as one of the largest global providers and developers of medical radioisotopes for this novel therapy.

Radiopharmaceutical Therapy has emerged as a promising, targeted cancer therapy with the potential to reduce the risk of both short- and long-term treatment effects while proving effective at detecting and killing the smallest deposits of cancer cells throughout the body. As such, the radioisotopes used in these treatment regimens have become precious commodities, and the quick rise in their demand means that companies are met with new challenges in terms of optimising their manufacturing and supply capabilities. As a global leader in this space, ITM ensures its ability to supply over 600 clinics in more than 60 countries with sophisticated production and distribution methods.



Manufacturing process of n.c.a Lutetium-177

ITM's Production Capacities

Radioisotopes must maintain a certain level of activity to be effective. This means that ITM only has a narrow window (24-48 hours within Europe, max. 72 hours for the rest of the world) in which to deliver. Additionally, radioisotopes cannot be pre-produced and stored. Each patient dose is filled with the ordered amount of activity for one treatment.

ITM has established a strong manufacturing position to meet these rigorous requirements and to serve a growing number of patients. The company recently opened NOVA in Neufahrn, near Munich, the world's largest production site of Lutetium-177, a novel medical radioisotope used in targeted cancer therapies. NOVA is located near the company's existing manufacturing facility in Garching and will increase ITM's already robust capacity to supply clinics, pharmaceutical partners, and its own pipeline.

A Strong Team is Essential

Beyond having the right production facilities in place, ITM has to react quickly to spikes in demand and handle any potential roadblocks. The team has established a global reactor network to be able to switch to other facilities in the unlikely event of outages. Many tasks are also supported by digital solutions, including ITM's self-programmed planning system which is capable of taking half-lives into account.

The company's success is based, above all, on its expert employees, who find creative solutions to sudden problems and collaborate to ensure orders for radioisotopes are fulfilled in a timely and efficient manner. ITM often receives and reacts to orders that are placed only one week to a few days before a patient starts treatment. In a system as fluid and multi-layered as a radiopharmaceutical supply chain, this human element remains essential. The ITM team takes its responsibility seriously to ensure that as many cancer patients as possible have access to promising radiopharmaceutical treatments worldwide.

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Don't despair! Pharma will come knocking again

VENTURE CAPITAL The mood is ambivalent. Depending on who you talk to, you hear old laments or "the turnaround is here". Last year was indeed one of the most difficult biotech years, what will 2024 bring? Is there light on the horizon? Olivier Litzka, Andera Partners, discusses the situation and new trends with EUROPEAN BIOTECHNOLOGY.

EuroBiotech_Dr Litzka, what is your view of the last year?
Olivier Litzka_*2023 was difficult for many biotech companies. This came as no surprise to those who've been around for a while and have watched the industry in Europe develop. The high mark set by the pandemic in 2021 was bound to lead to a setback. But last year was very good for M&A of advanced products in established, publicly listed companies. This may be the beginning of a new dawn, a trend reversal. The entire industry is beginning to work its way out of the trenches.*

EuroBiotech_So no reason to despair?
Litzka_*The fundamentals have not changed. The patent cliff, losing of market exclusivity, is still a reality. Between US$400 to 500bn will be affected by these patent losses. This is also one reason for the recent late-stage M&A boom in pharma. And what is true for pharma is also true for medtech. One example is Axonics, a company Andera Partners co-founded in 2012 and have supported for many years. It was recently acquired by Boston Scientific for a multi-billion-dollar sum. So, industry players are doing everything they can to compensate for the coming loss of sales. Of course, biotechs with an early pipeline are having a harder time at the moment because they lack the promise of sales in the short-term. But when late-stage pipelines have been filled and sales of drugs currently on the market have landed, pharma will come knocking on the doors of the early companies again.*

DR. OLIVIER LITZKA Partner with Andera Partners, office Munich-Martinsried, has longtime experience in venture investments.

EuroBiotech_It sounds like more of a waiting game. But isn't that precisely what is difficult for biotech companies short of funding?
Litzka_*From a global perspective, pharmaceutical companies shy away from taking major risks. A technology, a target, must first be validated and have impressive clinical results. Then a wave of interest often begins, as we are now seeing with obesity. Pharma is only buying projects with manageable risk. When this sentiment changes, very early candidates will become of interest again, and the familiar cycle of our industry will return. The takeover of Calypso, for example, is a first sign in this direction. It shows that pharma sees itself as sufficiently risk-balanced to get back in the game early.*

EuroBiotech_In this environment, are deals taking longer for biotechs with an earlier stage pipeline?
Litzka_*All VCs have looked very closely at their portfolios in recent months, and we have kept the money together to avoid jeopardising cash reach. But we also have good reserves. Yes, we have to get through a lean period because we don't have as much opportunity to exit via the stock market. As I said, pharma has been acquiring more mature, publicly listed companies than private ones or companies from the VC portfolio. There are some exceptions, such as Reviral for us and Emergence Therapeutics for others. It is difficult for biotech companies and for investors to determine the exit path, given the limits on entering into IPO negotiations.*

EuroBiotech_But a sale to pharma is allways a possibility for you?
Litzka_*Of course, but keep in mind companies are now being bought off the stock market for several billions. If there are fewer exciting stories there, then the focus will return to private companies, which can be purchased more affordably. VC funds also earn a return from sales to pharma, it doesn't have to be an IPO.*

EuroBiotech_Nevertheless, the IPO is considered the peak of a company's corporate development. Do we need an IPO boost for a lasting turnaround?

Picture: © Andera Partners

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Litzka_*The open IPO window is important for the entire ecosystem. But that depends on many things. When interest rates are high, generalist investors invest less in tech and therefore biotech shares, and more in other lucrative asset classes. If the central banks give indications that interest rates are more likely to fall again, then the machine starts up. You can see what has happened on the US stock market in recent weeks.*

EuroBiotech_Does this money and the revitalisation of the "machine" extend to Europe? Is there enough exciting science and tech here?

Litzka_*It always comes in waves. We have just seen major US financing in Europe. Then there was a small pause, but that's not so bad, because seeing financing on the scale we saw before Corona is a positive sign. We need to get the exaggerated expectations set during the pandemic out of our minds. And yes, you can find a lot of innovation in Europe. I would even say that one would have to think very long and hard to find a kind of innovation that doesn't exist here.*

EuroBiotech_ On the other hand, you get the feeling that a lot is going in the direction of China at the moment, bypassing Europe a bit, in some cases a kind of shopping spree of European pharma is taking place in China. Why is there this particular drive towards China?

Litzka_*Yes, I can see that too. Chinese companies initially focussed on copycat versions, but better than the original. A me-too but better. And if something like that works, this copy is possibly a best-in-class. Many Chinese companies are still doing this, and doing it very well. But we are also seeing more and more really new science from China. What has changed now is that Chinese companies want to do deals. Two years ago there was less of that. Now we have very active business development from Chinese companies offering a wide range of very good molecules.*

EuroBiotech_Is it resaonable to be afraid that all the deals will become agreed almost exclusively with China? In other words, that funding here could decline?

Litzka_*A fear of this would be exaggerated. Interactions with Chinese companies are not always easy, you need a very good basis of trust, but it can happen. For example, we have an excellent cooperation with a Chinese company in the medtech sector.*

EuroBiotech_Back to Europe. What makes you optimistic about the future?

Litzka_*We have not seen a corporate crisis here in the biotechnology sector. These have been difficult times, but there has not been a wave of bankruptcies; people have tightened their belts and focussed more on what is feasible. Perhaps some companies will continue to have difficulties in the coming months, perhaps we will still have a certain reluctance in terms of start-ups and seed financing. But Germany has the HTGF for these early-stage companies, which does a great job and makes it much easier to get started. The HTGF then needs follow-up financing and growth financing from VCs like us and other capable investors. But I also think that this will become easier again this year. On the side of institutional investments in VC funds, KfW Capital has the excellent instrument of the Future Fund in its hands. I think Europe's biotech market has found its bottom.*

EuroBiotech_Let´s have a look into your portfolio. As we focus on radiopharmacy in this issue, what led to the decision to invest in Ariceum therapeutics?

Litzka_*In April of 2023 Andera Partners co-led a series A extension round totalling €47.75m for Berlin-based radiopharmaceutical company Ariceum Therapeutics. Andera had been looking at the radiopharmaceuticals field some years ago but until recently, it seemed too early to invest. It was the involvement of big pharma in the sector—particularly Novartis and Bayer—that really helped spark progress in the sector. Ariceum was the right investment for us because it already has a program in the clinic. It also has high ambitions and a great team.*

EuroBiotech_What specifically helped spark the progress?

Litzka_*Radiopharmaceuticals can be difficult to produce, distribute and administer. The molecules work by binding to surface proteins on certain cancer cells in order to deliver radioactive isotope directly to the cancer cells. Two very successful products marketed by Novartis proved that the approach works.*

EuroBiotech_What is the market potential in your view?

Litzka_*In small cell lung cancer, between 60-80% of patients have the target protein at which Ariceum's lead product is aimed. We estimate that sales from this product to generate €800-900m per year. A more optimistic calculation would be up to €1.5bn per year. This may sound like a lot but Novartis expects €2bn for the neuroendocrine tumours indication.* ■

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Radiolabled portfolio

Andera portfolio company Ariceum Therapeutics launched in 2021, after acquiring all rights to a clinical program from Ipsen which remains a shareholder.

› Its lead targeted systemic radiopharmaceutical product, 177Lu-satoreotide tetraxetan ("satoreotide") is an antagonist of the somatostatin type 2 (SST2) receptor which is overexpressed in neuroendocrine tumours (NETs), some aggressive cancers such as small cell lung cancer (SCLC) and the childhood cancer, neuroblastoma.

› Satoreotide is being developed as a 'theranostic' pair for the combined diagnosis and targeted radionuclide treatment of these tumours ■

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WHERE FUTURE BECOMES REALITY

Are there bright times for biotech IPOs ahead?

PETER THILO HASLER, FOUNDER AND RESEARCH ANALYST OF SPHENE CAPITAL Despite the recent stock market rally and declining volatility, IPOs are rather rare in many industrialised countries – not least for seasonal reasons. The main reason for this, however, is the aggressive monetary policy of the central banks, with more than ten interest rate hikes in both Europe and the US.

As inflation has weakened significantly worldwide this year, a turnaround in interest rates cannot be completely ruled out, which in turn should boost activity on the primary markets. This is already evident in the USA, where eight biotechnology companies have gone public in the first few weeks of the year: Cancer drug developers ArriVent BioPharma and CG Oncology, diabetes and obesity drug developer Fractyl Health, psychiatric drug maker Alto Neuroscience, autoimmune company Kyverna Therapeutics, pain treatment company Chromocell Therapeutics, small molecule developer Telomir Pharmaceuticals, and gene-editing firm Metagenomi. Some of them had a surprising post-IPO-share price performance, especially CG Oncology, which went public at the Nasdaq Global Select Market at US$ 19.00 per share and is now trading at US$ 47.93 per share, a +152.3% increase.

Although it´s still early days in a new year: Biotech companies are among the year's best-performing debutants in an otherwise choppy IPO market that has seen mixed pricing for many IPOs. Many retail investors who seem to have suddenly realised three years ago that drug making could be risky, are not used to these figures. From this perspective, 2024 could mark the end of the biotechnology IPO drought.

But despite sustained signs of life for the first time in years, the window is not open yet, at least not for all biotechnology companies and not everywhere. While on average, the share price performance of US biotechnology IPOs was 18.6% to date, preclinical IPOs performed worse, with -12.1%, than those in their clinical stage, with +37.0%.

This is an indication that investors remain selective and skewed towards late-stage, de-risked types of assets, those with clinical data available. European biotech companies intending to go public should keep in mind that it is a company's job to show proof of concept in patients. Going public beforehand means accepting substantial valuation discounts, especially in Europe. ■

News from the floor

Argenx BV, had a rollercoaster year in 2023, with shares rising about 40% after a positive trial result in July and then falling as much as 29% after a negative result from another trial published in December. The company from The Netherlands is trying to expand the use of its immunology drug Vyvgart to other diseases. It is used to treat a rare chronic immune disorder called myasthenia gravis, which causes muscle weakness.

Bayer AG, (FWB: BAYN) has a lot of troubles in managing billions of debt and litigations in the USA stemming from the acquisition of US Monsanto. New CEO Bill Anderson is trying to get its debt under control with a strict cost-cutting programme. This has now also been felt by the shareholders, who have had to endure a tough cut in the dividend in conjunction with a historically poor share price.

CRISPR Therapeutics Inc., Switzerland/US (Nasdaq: CRSP) having approvals of first gene-editing-based medicines for sickle cell anemia in the pocket, announced the sale of its common shares to a select group of institutional investors in a registered direct offering, snagging approximately US$280m.

Formycon AG, biosimilar developer in Munich, Germany (FWB: FYB) announced that Hungary based specialty pharmaceutical company Gedeon Richter Plc. becomes strategic investor via a cash capital increase from authorised capital in the amount of 9.08% of its share capital, where also billionairs Strüngmann are invested. ■

Picture: © Sphene Capital

COMPANY	QUOTE	M-CAP	52 WEEKS INDICATOR low high
2cureX AB	0,13	2,300k	
4SC AG	2,98	30,100k	
AB Science SA	3,00	115,200k	
Abcam plc	11,83	3,000,000k	
Abionyx Pharma SA	1,13	3,600k	
Abivax SA	13,58	836,700k	
Ablivia AB	0,02	1,700k	
AC Immune SA	3,41	341,200k	
Acticor Biotech SA	4,85	65,400k	
Active Biotech AB	0,05	13,600k	
Adaptimmune Therapeutics plc	1,55	343,000k	
ADC Therapeutics SA	4,37	38,100k	
Addex Therapeutics Ltd	0,07	8,500k	
ADL Bionatur Solutions SA	0,32	57,900k	
Adocia SAS	10,08	139,600k	
Advicenne SA	1,30	16,500k	
Aelis Farma SAS	13,45	178,300k	
Affimed NV	0,46	71,000k	
Akari Therapeutics plc	2,14	32,300k	
ALK-Abelló A/S	17,33	3,470,000k	
Alkermes plc	27,60	4,610,000k	
Allarity Therapeutics A/S	0,37	2,100k	
Alligator Bioscience AB	0,10	62,800k	
Altamira Therapeutics Ltd	2,86	4,800k	
Alvotech SAS	16,05	4,060,000k	
Alzinova AB	0,17	7,900k	
Amniotics AB	0,00	500k	
Annexin Pharmaceuticals AB	0,02	7,600k	
Aprea Therapeutics AB	6,04	23,400k	
Aqua Bio Technology ASA	0,36	55,200k	
Arctic Zymes Technologies ASA	2,51	127,700k	
Arecor Therapeutics plc	1,65	30,600k	
Argenx BV	377,70	22,300,000k	
Arocell AB	0,03	230,100k	
Arterra Bioscience SpA	1,81	12,000k	
Asarina Pharma AB	0,32	1,800k	
Ascelia Pharma AB	0,60	22,100k	
Ascendis Pharma A/S	144,00	8,366,700k	
Autolus Therapeutics plc	5,95	1,306,100k	
Avacta Group plc	1,06	279,800k	
Avadel Pharmaceuticals plc	11,80	1,073,600k	
Axichem AB	0,12	2,600k	
Basilea Pharmaceutica AG	37,65	449,300k	
Bavarian Nordic A/S	23,15	1,730,000k	
Bergenbio ASA	0,02	46,800k	
Bicycle Therapeutics plc	23,60	739,000k	
Bioarctic AB	19,71	1,450,000k	
Biocartis NV	0,26	24,700k	
Bioextrax AB	0,20	5,100k	
Biofrontera AG	0,33	22,300k	
Biogaia AB	11,20	1,090,000k	
Bioinvent International AB	1,47	65,800k	
Biomed-Lublin SA	0,22	15,700k	
Biomérieux SA	105,15	12,200,000k	
BioNTech SE	86,40	20,600,000k	
Biophytis SA	0,00	4,000k	
Bioporto Diagnostics A/S	0,22	379,700k	
BioSenic SA	0,01	5,100k	
Biosergen AB	0,07	3,200k	

COMPANY	QUOTE	M-CAP	52 WEEKS INDICATOR low high
Biotage Sweden AB	15,09	1,200,000k	
Bioventix plc	57,00	287,100k	
Biovica International AB	0,21	16,700k	
Bioxxmed AG	0,32	1,600k	
Bivictrix Therapeutics plc	0,13	82,500k	
Brain AG	3,99	87,200k	
C4X Discovery Holdings plc	0,13	32,300k	
Calliditas Therapeutics AB	9,50	583,300k	
Camurus AB	39,78	2,300,000k	
Cantargia AB	0,25	43,900k	
Carbios SAS	24,50	427,700k	
Cellectis SA	2,34	187,200k	

Cellink AB	3,89	284,500k	
Celon Pharma SA	3,42	174,400k	
Celyad Oncology SA	0,33	9,700k	
Centessa Pharmaceuticals plc	10,50	1,023,600k	
Centogene NV	0,71	20,200k	
Circio Holding	0,53	4,100k	
Cline Scientific AB	0,01	400k	
Co.don AG	0,02	300k	
Coegin Pharma AB	0,02	9,400k	
CombiGene AB	0,31	6,500k	
Cosmo Pharmaceuticals NV	73,16	1,217,000k	
CRISPR Therapeutics AG	78,00	6,820,000k	
CSL Ltd	170,30	83,148,600k	
Curevac NV	3,21	737,700k	
Cyxone AB	0,02	300k	
DBV Technologies SA	1,40	134,500k	
Destiny Pharma plc	0,41	39,400k	
Diagonal Bio AB	0,03	1,700k	
Diamyd Medical AB	1,17	100,200k	
Diasorin SpA	95,20	5,080,000k	
DMS Imaging	0,02	30,500k	
Elicera Therapeutics AB	0,14	2,800k	
Ellen AB	0,13	600k	
Enzymatica AB	0,26	43,500k	
Epigenomics AG	1,63	1,500k	
Erytech Pharma SA	2,73	18,200k	
e-Therapeutics plc	0,16	95,800k	
Eurobio Scientific SA	16,98	171,200k	
EurocineVaccines AB	0,00	200k	
Eurofins Scientific SE	55,58	10,070,000k	
Evaxion Biotech A/S	3,47	16,600k	

COMPANY	QUOTE	M-CAP	52 WEEKS INDICATOR low high
Evgen Pharma plc	0,00	1,100k	
Evolva SA	0,66	3,100k	
Evotec SE	13,88	2,483,800k	
Expres2ion Biotech Holding AB	0,30	15,200k	
Faron Pharmaceuticals Oy	1,56	68,800k	
Fermentalg SA	0,67	26,700k	
Fluicell AB	0,02	6,400k	
Formycon AG	49,80	794,700k	
Fusion Antibodies plc	4,77	2,800k	
Gabather AB	0,05	700k	
Galapagos NV	33,59	2,220,000k	
Genedrive PLC	0,05	6,500k	
Geneuro SA	1,30	37,400k	
Genfit SA	3,33	165,500k	
Genflow Biosciences plc	0,01	4,200k	
GENinCode plc	0,04	700k	
Genmab A/S	269,50	17,604,600k	
Genomic Vision SA	0,00	600k	
Genovis AB	3,53	231,100k	
Genoway SA	3,96	37,000k	
Gensight Biologics SA	0,39	25,400k	
Gentian Diagnostics AS	3,45	53,200k	
Genus plc	23,02	1,470,000k	
Global Bioenergies SA	1,93	34,900k	
Glycorex Transplantation AB	0,24	16,900k	
Guard Therapeutics International AB	0,16	1,600k	
Hansa Biopharma AB	2,89	152,100k	
HBM Healthcare Investments AG	165,00	1,150,000k	
Heidelberg Pharma AG	3,04	143,100k	
Hemogenyx Pharmaceuticals plc	0,04	41,100k	
Herantis Pharma Oyj	1,17	24,900k	
Hofseth Biocare ASA	0,21	81,200k	
Hookipa Biotech AG	0,59	49,800k	
Hybrigenics SA	0,01	5,500k	
Idorsia Ltd	3,05	584,200k	
Immatics NV	11,24	1,150,000k	
Immunic AG	1,17	109,700k	
Immunovia AB	0,12	6,500k	
Immupharma plc	0,01	4,600k	
Index Pharm. Holding AB	0,02	13,200k	
Infant Bacterial Therapeutics AB	7,94	102,000k	
InflaRx NV	1,40	79,600k	
Innate Pharma SA	2,40	192,900k	
Integragen SA	0,85	5,700k	
Intervacc AB	0,29	21,700k	
Inventiva SA	3,05	157,400k	
IO Biotech Inc.	1,39	93,700k	
IRLAB Therapeutics AB	1,32	66,800k	
Isofol Medical AB	0,04	5,900k	
ISR Holding AB	0,12	8,000k	
Kancera AB	0,18	16,100k	
Kuros Biosciences AG	5,64	211,300k	
Lipigon Pharmaceuticals AB	0,03	2,500k	
Lipum AB	0,78	7,300k	
Lytix Biopharma AS	0,54	21,400k	
MaaT Pharma SA	7,20	90,600k	
Mabion Ltd	4,29	69,400k	
Mainz Biomed BV	0,86	13,700k	
Marinomed Biotech AG	22,90	34,700k	

COMPANY	QUOTE	M-CAP	52 WEEKS INDICATOR low high
MDxHealth SA	2,89	82,300k	
Medesis Pharma SA	0,80	3,600k	
Medigene AG	1,51	36,200k	
Medincell SA	8,94	263,700k	
Medivir AB	0,02	2,500k	
Mendus AB	0,04	27,000k	
Merus BV	43,20	2,490,000k	
Metabolic Explorer SA	0,36	18,400k	
Mithra Pharmaceuticals SA	0,53	35,900k	
Modus Therapeutics Holding AB	0,14	5,100k	
Molecular Partners AG	4,00	134,200k	
Morphosys AG	65,32	2,450,000k	
Nabriva Therapeutics plc	1,25	4,000k	
Nanobiotix SA	6,01	284,100k	
Newron Pharmaceuticals SpA	9,47	172,300k	
Nextcell Pharma AB	0,17	6,000k	
NFL Biosciences SA	2,07	16,200k	
Nicox SA	0,44	21,900k	
Niox Group plc	0,69	292,400k	
NLS Pharmaceutics AG	0,37	12,900k	
Novacyt SA	0,52	37,900k	
Novozymes Biopharma DK A/S	52,29	21,375,300k	
NuCana ADR	0,28	14,700k	
Nykode Therapeutics ASA	1,58	515,000k	
Nykode Therapeutics ASA	1,57	513,700k	
ObsEva SA	0,06	5,500k	
Okyo Pharma Ltd	1,30	43,800k	
Oncimmune Holdings plc	0,21	15,400k	
Oncoarendi Therapeutics SA	4,59	77,300k	
Oncopeptides AB	0,47	42,100k	
OncoZenge AB	0,36	4,200k	
Open Orphan plc	0,31	213,600k	
Optibiotix Health plc	29,50	23,400k	
Orphazyme A/S	167,00	6,000k	
Oryzon Genomics SA	1,87	116,000k	
OSE Immuno SA	3,42	73,900k	
Ovoca Bio plc	0,99	200k	
Oxford Biodynamics plc	15,38	31,900k	
Oxford Biomedica plc	0,16	32,800k	
Oxurion NV	0,00	1,600k	
Paion AG	0,06	300k	
Pangaea Oncology SA	1,82	55,500k	
PCI Biotech Holding ASA	0,15	5,800k	
Pharma Mar SA	32,68	594,000k	
Pharming Group NV	1,05	699,300k	
Pharnext SA	0,51	100k	
Photocure ASA	4,73	128,200k	
Physiomics plc	0,01	2,000k	
Pieris Pharmaceuticals Inc.	0,15	15,100k	
Plant Advanced Technologies SA	4,48	4,900k	
PMD Device Solutions AB	0,90	17,700k	
PolyPeptide Laboratories (Sweden) AB	17,24	575,200k	
Polyphor AG	0,18	10,300k	
Poolbeg Pharma plc	11,79	60,500k	
Poxel SA	0,43	17,400k	
Predilife SA	4,26	15,900k	
Probi AB	18,00	207,200k	
ProQR Therapeutics BV	1,97	156,100k	
Prostatype Genomics AB	0,00	3,400k	

COMPANY	QUOTE	M-CAP	52 WEEKS INDICATOR low high
Proteome Sciences plc	0,06	17,100k	
Prothena Corporation plc	26,00	1,391,800k	
Pure Biologics SA	2,01	6,600k	
Qiagen NV	40,00	8,850,000k	
Q-Linea AB	0,20	24,700k	
Quantum Genomics SAS	0,10	3,500k	
Redx Pharma plc	0,21	80,900k	
Relief Therapeutics Holding AG	1,74	18,700k	
Reneuron Group plc	0,03	1,900k	
Ryvu Therapeutics SA	13,32	308,000k	
Saniona AB	0,15	16,600k	
Santhera Pharmaceuticals AG	11,63	120,600k	
Sareum Holdings plc	0,41	29,100k	
Scancell Holdings plc	0,09	84,000k	
Scandion Oncology A/S	0,20	8,000k	
Selvita SA	13,32	244,500k	
Sensorion SA	0,94	265,200k	
SenzaGen AB	0,54	13,300k	
Shield Therapeutics plc	3,08	24,100k	
Silence Therapeutics plc	23,56	928,500k	
Simris Alg AB	0,00	100k	
Skinbiotherapeutics plc	11,34	21,600k	
Softox Solutions AS	0,10	1,000k	
Sophia Genetics SA	4,52	285,800k	
Sprint Bioscience AB	0,07	5,800k	
Stayble Therapeutics AB	0,02	700k	
Summit Therapeutics plc	3,77	2,871,200k	
Swedish Orphan Biovitrum AB	22,76	7,750,000k	
SynAct Pharma AB	0,72	24,400k	
Synairgen Research Ltd	0,06	12,100k	
Theradiag SA	0,06	16,600k	

COMPANY	QUOTE	M-CAP	52 WEEKS INDICATOR low high
Theranexus SA	0,72	5,400k	
Thor Medical ASA	0,09	21,500k	
Tissue Regenix Group plc	93,94	68,400k	
Tiziana Life Sciences plc	0,47	48,300k	
TME Pharma NV	0,34	2,300k	
Transgene SA	1,05	103,800k	
Trinity Biotech plc	2,14	15,500k	
Ultimovacs ASA	12,65	409,400k	
uniQure NV	5,96	285,000k	
Valbiotis SAS	4,12	4,500k	
Valerio Therapeutics	0,12	18,800k	
Valirx plc	0,46	446,400k	
Valneva SE	3,29	446,400k	
VectivBio AG	15,45	963,300k	
Verici Dx plc	0,14	32,400k	
Verona Pharma plc	15,14	1,113,000k	
Vicore Pharma Holding AB	1,19	135,900k	
Virax Biolabs Group Ltd	0,82	2,000k	
Virogates A/S	1,11	6,300k	
Vita 34 AG	4,90	86,300k	
Vivoryon Therapeutics AG	4,90	210,700k	
WntResearch AB	0,00	4,000k	
X4 Pharmaceuticals Inc.	0,88	146,400k	
Xbrane Biopharma AB	0,08	2,200k	
Xintela AB	0,02	12,400k	
Xlife Sciences AG	3,67	87,200k	
Xspray Pharma AB	3,96	96,400k	
Zealand Pharmaceuticals A/S	95,05	4,970,000k	

All quotes are listed in Euro. All data is provided without guarantee. The effective date is 27th February 2024.
These Europe-based biotech companies are traded on European stock markets.

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Rejuvenation assembly

LONGEVITY A new foundation from Saudi Arabia is preparing to invest billions in longevity research. The foundation, called Hevolution and headed by Mehmood Khan, is based in Riyadh, but also wants to influence the western world, the USA and Europe.

The application deadline for research funding as part of the Hevolution Foundation's second call for innovation closed at the end of February. Up to 20 projects are to be funded with SAR 500,000 (around 120,000 euros) each.

Established in 2021, the Hevolution Foundation is the first global non-profit organisation of its kind to provide grants and early-stage investments to incentivise independent research and entrepreneurship in the emerging field of health sciences. It plans to invest more than US$1 billion per year in global longevity efforts.

Playing big

Included in the US$1bn investment per year in global longevity efforts is providing such grants but also early-stage investments to incentivise independent research and entrepreneurship in the emerging field of health sciences. The foundation already set foot with a North American centre and plans to open offices in other global locations, to achieve some of the foundation´s goals:

- Increasing the number of longevity researchers worldwide
- Increasing the number of companies working in this field
- Attracting funding to the field of ageing.

Hevolution is not the only foundation in the anti-ageing arena, but they put the most money in. The longevity research movement is steadily gaining momentum. California is now home to the first research centre dedicated exclusively to healthy ageing. California is also the place, where the early approaches of understanding ageing started some 25 year ago.

Michael Greve, founder of Forever Healthy Foundation. He will open the second edition of Rejuvenation Startup Summit to be held in Berlin 10th–11th of May.

But it took a decade until the scientific community realised that there might be a grain of truth in the early postulates of living beyond 120 years of age. Many different scientist developed the concept of 'hallmarks of ageing', where some molecular changes are bringing the organism to accumulate errors, leading to disease. All of these hallmarks are connected and increasing evidence has now led to a common understanding of at least some mechanisms and their regulation. Not at last the progress with groundbreaking developments such as iPSCs, Yamanaka-factors of stem cell research, CRISPR, AlphaFold, and CAR-T and checkpoint inhibitors have boosted the sector.

European assembly

In Europe the Forever Healthy Foundation, Kizoo Capital, and Maximon (among others) are actively shaping the ecosystem.

The main issue is still to get funding for new breakthrough ideas. That´s why the Rejuvenation Startup Summit again assembles in Berlin with investors and researchers.

Eric Verdin, CEO of the Buck Institute for the Biology of Aging in Novato, California, will represent the first independent biomedical research institute in the world focused solely on aging. The Buck is a collective of the world's top scientists in the field of aging who are sharing their methods and expertise.

With the second edition of the event, following the inaugural Summit in 2022 with more than 400 participants from over 30 countries, latest developments in the field will be discussed and many international start-ups get on stage. Mehmood Khan, head of Hevolution foundation, will be watching and presents the Saudi Arabian approach to healthier ageing. ■

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Morphosys sold for €2.7bn to Novartis

ACQUISITION Morphosys, Planegg/Munich (Germany), opted for a takeover rather than wait for approval, which is fraught with uncertainty. Novartis CEO Vas Narasimhan was looking for assets in the low billion-dollar range and acquired a pipeline derived from the US company Constellations Pharma, which had been incubated in Bavaria for several years.

Headquarter of Morphosys, changing the company flags soon

The former antibody platform developer in Planegg, close to Munich, had the interest of the community on its side in mid-November, publishing topline data of its clinical Phase III for Pelabresib

This drug was incorporated in a transformative move of Morphosys by buying US company Constellations Pharma in 2021 for about US$1.7bn and putting their own antibody pipeline aside. Based on the data, the biotech company intends to apply for marketing authorisation in the USA and Europe next year. But the reception of the news was quite mixed as Pelabresib in combination with Ruxolitinib did not provide good data in an important secondary endpoint (TSS50) compared to placebo plus Ruxolitinib.

TSS50 was achieved at week 24 in 52% of patients in the Pelabresib plus Ruxolitinib-treated group compared to 46% in the Placebo plus Ruxolitinib-treated group. With this low difference in patient response however, many analysts see a real risk that the FDA and EMA will not grant approval as authorities attach great importance to TSS50 as a secondary endpoint. The shares went south dramatically.

Hopes revived

In the new year, share price of Morphosys slowly recovered, but the rumour mill began to bubble slightly at the end of January that a take over could be the best bet for the future of Morphosys.

This happend rather fast early in February with the signature of an agreement to be acquired by Novartis for an equity value of €2.7 billion. Novartis wanted to launch a voluntary public tender offer for all Morphosys shares at a price of €68.00 per share in cash. According to Morphosys, this is an "attractive premium of 94% on the volume-weighted average share price of the last month before January 25 of 2024". However, this does not significantly exceed the share price performance of the last few days, as the share price was already around €67 because of the roumours. The increase in market capitalisation is also manageable. Just in the first few days of the new year, before the share price gained momentum, this was around €2bn.

Novartis has the "extensive resources necessary to fully develop and expand the potential of Pelabresib on a global scale", said the Morphosys Executive Board and Supervisory Board in justifying the sale, which was unanimously approved. There was another bidder, cooperation partner Incyte, who will not go away empty-handed, but will receive all rights to the antibody tafasitamab (Monjuvi), which has been marketed by both companies to date and is being developed for other indications.

US molecules on the way home

For observers, it is a rather rare spectacle that US born active ingredients (have to) take a diversion via Europe or Germany in order to end up with a pharmaceutical company that is strongly focussed on the US market. Although Novartis is based in Switzerland, business development and innovation deals are mainly conducted in and for the USA. For the records: The best Morphosys antibody ever reaching approval is Tremfya (J&J/Janssen), with sales reaching several billions per year. But this 'licensing constellation' was cut in favour of the merger with Constellation. ■

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Curious2024 – Future Insight™ conference

INNOVATION From July 10th to 11th, the multidisciplinary Curious2024 – Future Insight™ Conference is bringing together some of the world's brightest scientists, including several Nobel laureates, and the most accomplished innovators to present their work and explore the future of science and technology, solving the challenges of today and enabling the dreams of a better tomorrow.

Explore diverse topics from health, nutrition, synthetic biology, materials, energy, digitisation, artificial intelligence, machine learning, robotics, mobility, space flight, to secrets of the human mind and new ways of working together. The conference is a platform where Nobel laureates and top scientists share their latest breakthroughs. Past attendees have called it the 'Woodstock of science' and praised it for its energizing and diverse offerings.

In addition to the rich scientific content, the conference is also known for its incredible networking opportunities. You will have the chance to interact with strategic partners, exhibitors, and sponsors, such as NATURE and AAAS/SCIENCE, who share a common vision for the transformative power of science and technology. The conference also features the Future Insight™ Prize, awarded to honor outstanding achievements in science and technology that help to realise visionary products important for humanity.

Don't miss this chance to be a part of a community united by science for a better tomorrow, keeping inspired and excited for the future. We look forward to seeing you at Curious2024 – Future Insight™ Conference, happening from July 10–11 in Mainz, Germany, and online as a hybrid event.

Contact us:
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Frankfurter Strasse 250
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www.curiousfutureinsight.org/
Tickets : www.curiousfutureinsight.org/tickets/

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New cell therapies in cancer

IMMUNOTHERAPY CAR-T cell therapies have revolutionised the treatment of liquid tumours. With the FDA approval of the first T cell therapy for solid tumors, TILs and TCR-Ts are in the spotlight. Now, there are solutions for addressing challenges with solid tumours.

The advent of Chimeric Antigen Receptor (CAR)-T cell therapies, highly effective cell therapies for certain types of liquid tumors, was a truly groundbreaking step. Today, six CAR-T products have been approved for the treatment of liquid tumors, malignant cells that originate in the bone marrow, such as leukemias and lymphomas. Recently, the FDA approved the first cell therapy for a solid tumor, Iovance's Amtagvi for the treatment of metastatic melanoma. Amtagvi is not a CAR-T therapy but uses a patient's unmodified tumor-infiltrating lymphocytes (TILs). Another form of adoptive cell therapy, T Cell Receptor T Cell (TCR-T) therapies, also holds high promise in overcoming the barriers for treating solid tumours

Hidden antigens

In contrast to solid tumours, liquid tumours are often characterised by specific cell surface markers, easily accessible targets for CAR-T cells. These therapies are generated by isolating a patient's T cells and introducing a CAR, a chimeric receptor that directly recognises antigens on the cell surface.

However, the efficacy of CAR-T cells against solid tumours is hampered by the lack of distinct cell surface markers, which prevents specific targeting without risking significant on-target/off-tumor effects. To address this challenge, alternative cell therapy modalities target intracellular antigens that are hidden from CAR-T cells.

TCR-T cells, a promising approach for targeting such hidden antigens, are patient-derived T cells engineered with naturally occurring or minimally modified TCRs. TCRs recognise their targets only in the context of a major histocompatibility complex (MHC) molecule, which can present fragments of virtually any cellular protein. By selecting or engineering TCRs that precisely recognise solid tumour antigens, TCR-T cells have the potential to effectively attack solid tissue while reducing the risk of off-target toxicities.

The recently FDA-approved Amtagvi relies on recognition of a mix of tumour antigens by using a patient's unmodified heterogeneous set of T cells isolated from the tumour, activating them, and returning these activated TILs back to the patient. This approach uses the patient's natural T cell repertoire against the tumour which may target both intracellular and extracellular tumour antigens.

Overcoming TME

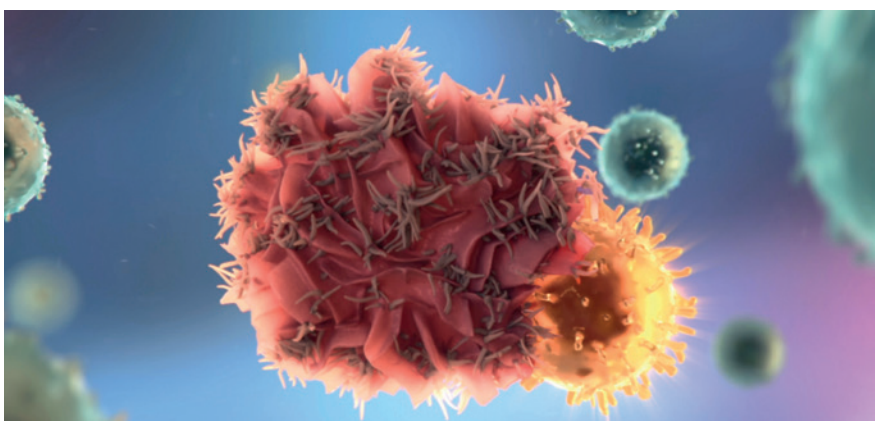
Additionally, solid tumours manage to avoid recognition by the immune system by creating an immunosuppressive tumour microenvironment (TME).

One strategy is to express molecules that activate immune checkpoints and thereby suppress the immune response. Immune checkpoint inhibitors, most notably PD-1/PD-L1 inhibitors, counteract these immunosuppressive signals and allow for better immune cell activation. Combination of cell therapies with immune checkpoint inhibitors would be one way around this. Another option is to directly enhance TCR-T cells to overcome the immunosuppressive TME. For instance, German company Medigene uses a costimulatory switch receptor PD1-41BB that is rewired to convert the immunosuppressive PD-L1 signal into an activating signal as part of its TCR-T technology platform.

Yet, immune checkpoints are only one part of the multifaceted TME. Therefore, several other approaches to overcome the TME are under investigation, focusing on enhancing T cell efficacy, promoting T cell proliferation, counteracting the physiological hurdles of the tumour microenvironment, addressing T cell exhaustion, and inducing the generation of memory T cells for a sustained immune response.

While cell therapies hold immense promise for the treatment of solid tumours, technological advancements are needed to overcoming such hurdles and unlocking the full potential of cell therapies in the fight against cancer. ■

g.kaeaeb@biocom.eu



Cancer cell attacked by T cells

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NEWS

Cancer stop

German **Bayer SE**'s US subsidiary **Vividion Therapeutics Inc** has initiated Phase I dosing evaluating the therapeutic window, pharmacological properties and safety of its oral STAT3 blocker VVD-130850 in patients with advanced solid and hematologic cancers. The drug candidate targets a novel allosteric pocket leading to direct inhibition of DNA binding and expression of STAT3 target genes in cancer cells.

Heading cancer market

BioNTech SE and **DualityBio Inc** have entered into a pivotal Phase III study with their ADC BNT323/DB-1303 that targets HER2 in metastatic breast cancer patients.

Cancer immunotherapy

French cancer antibody specialist **Biomunex Pharmaceuticals SAS** has announced the start of Phase I testing of OT-A201, a bispecific antibody targeting two non-public immune checkpoints. The candidate drug was licenced by Swiss **Onward Therapeutics SA** back in 2021 after preclinical results pointed tolexcellent specificity and safety, as well as in vivo tumour-killing activity at different doses. The first part of the ongoing study conducted by Onward Therapeutics is dedicated to dose finding in patients with advanced/metastatic solid tumours or relapsed/refractory hematological malignancies. The second part is an expansion study that will further evaluate the safety and preliminary antitumoral activity of the candidate as monotherapy or in combination.

Update of ongoing clinical trials

ANTIVIRALS

Viennese **G.ST Antivirals GmbH** has reported promising Phase I results of nasal 2-Deoxy-D-Glucose against upper respiratory tract infections in 45 healthy volunteers. The glucose analog prevented reproduction of rhino- and coronaviruses (RV) by blocking host glycolysis. The company announced that it has cashed in additional €6m from investors to carry out the subsequent Phase II clinical study, which will start enrollment in H1/2024. According to G.ST Antivirals, intranasal administration of either single ascending doses (SAD) or multiple ascending doses (MAD) of 3.5% 2-DG did not lead to serious adverse events (SAEs).

ASTHMA

British pharma giant **GlaxoSmithKline plc** is expanding its respiratory diseases drug portfolio. In February, the company announced that it was putting US$1bn upfront on the table to take over **Aiolos Bio Inc.**, which started with a US$232m Series A financing last year. The US$1.4bn (including milestones) deal gives London-based GSK asthma candidate AIO-001, a Phase II-ready, long-acting antibody that targets the regulatory human thymic stromal lymphopoietin (TSLP) ligand to relieve inflammation. GSK said AIO-001 could redefine the standard of care in asthma via the prospect of dosing every six months.

HIDRADENITIS SUPPURATIVA

Brussels-based **UCB SA** has presented promising results from post hoc analyses of its Phase III studies, BE HEARD I and BE HEARD in which the Brussels-based biopharma company evaluated the efficacy and safety of its approved IL-17A/IL-17F-blocking psoriasis antibody bimekizumab in adults with moderate to severe hidradenitis suppurativa, a inflammatory skin disease with systemic effects. With bimekizumab, the analyses showed that over 48 weeks, about 70% of patients improved by at least 55% in the International Hidradenitis Suppurativa Severity Score System (IHS4). The study included an initial (Weeks 0–16) and a maintenance treatment period (Weeks 16–48). Patients (n=1,014) were randomised 2:2:2:1 (initial/maintenance) to receive, either bimekizumab 320 mg every two weeks (Q2W)/Q2W (n=288), bimekizumab Q2W/Q4W (n=292), bimekizumab Q4W/Q4W (n=288) or placebo/bimekizumab Q2W (n=146). At Week 16, a greater proportion of patients achieved IHS4-55 with bimekizumab treatment vs placebo (51.1-62.9% vs. 25.7–30.8%). By Week 48, these responses were sustained or increased (pooled, 71.0–77.4%). Patients who switched from placebo to bimekizumab achieved comparable responses to those receiving continuous bimekizumab treatment (pooled, 76.2%).1 The higher thresholds of IHS4-75 and IHS4-90 (improvement of symptoms by 75% or 90%, respectively) were also achieved by greater proportions of patients treated with bimekizumab vs placebo at Week 16 (IHS4-75: 30.6–44.7% vs 15.7–23.1%; IHS4-90: 16.5–23.0% vs 7.1–10.8%). By Week 48, these responses were sustained or increased (IHS4-75 pooled, 56.0-61.9%; IHS4-90 pooled, 36.2-44.1%). At Week 16, patients treated with bimekizumab in the lowest (<2.40 years) disease duration quartiles achieved HiSCR50/HiSCR75 of 67.5% (n=133/197)/48.2% (95/197) vs 43.8% (n=14/32)/21.9%(n=7/32) for placebo. Patients treated with bimekizumab in the highest (≥10.87 years) disease duration quartiles achieved HiSCR50/HiSCR75 of 53.8% (n=99/184)/34.2% (n=63/184) vs. 28.9% (n=13/45)/20.0% (n=9/45) for placebo. Results with bimekizumab were sustained across 48 weeks of treatment.

AML

In eary February, the US cell therapy company **AvenCell Therapeutics**, which emerged from German **GEMoAb GmbH**, has treated the first out of up to 37 patient in a Phase Ia trial with AVC-201, a novel CRISPR-engineered allogeneic CD123-directed switchable CAR-T therapy for the treatment of relapsed/refractory acute myeloid leukemia and other CD123-overex-

pressing hematological malignancies. The multicentre trial, which aims to determine the maximum tolerated dose, efficacy, safety, and CAR-T persistence, is being conducted in Germany and the Netherlands.

CYSTIC FIBROSIS

In January, **Enterprise Therapeutics Ltd** has raised £26m for the Phase IIa trial of ETD001, a novel cystic fibrosis treatment, with investment led by **Panakes Partners** and participation from existing investors. ETD001 is a unique small molecule designed to target the ENaC ion channel, which plays a key role in airway hydration and mucus clearance. It promises to be a long-acting treatment that could significantly improve lung function in cystic fibrosis patients, particularly those who are either not eligible for or not receiving CFTR modulators.

HIV

Italian CDMO **ReiThera Srl**, the Ragon Institute of Massachusetts General Hospital, and non-profit scientific research organisation IAVI are collaborating to develop a novel HIV vaccine candidate that will be composed of ReiThera's gorilla adenoviral vector and HIV T cell epitopes identified by the Ragon Institute, funded by the Bill & Melinda Gates Foundation. According to the collab agreeement, ReiThera will perform vector engineering and generation, process development, and good manufacturing practice (GMP) manufacture while the Ragon Institute will lead GRAd-HIV preclinical development. The study will be sponsored by IAVI, which is set to execute a Phase I trial to evaluate the safety and immunogenicity of the GRAd-HIV vaccine.

PARKINSON/HEART FAILURE

Bayer SE's US gene therapy unit **Asklepios Biopharmaceutical Inc. (AskBio)**, made two announcements in January: Firstly, the company started enrollment of patients with congestive heart failure into a Phase II gene therapy trial with AB-1002 (NAN101), an AAV vector that encodes an protein phosphatase I blocker. Secondly, it annouced Phase Ib success with its Parkinson's gene therapy AB-1005 (AAV2-GDNF) over 18 months, which expressed the human glial cell line-derived neurotrophic factor (GDNF) after direct injection into the putamen. AskBio's gene therapy, was safe and well tolerated in patients with mild to moderate Parkinson's disease. AskBio is now planning a Phase II trial expected to begin in H1/2024.

OSTEOPOROSIS

Island-based biosimilar specialist **Alvotech SA**, has reported positive results from a Phase Ib pharmacokinetic study of its denosumab biosomilar AVT03. The study, which met its primary endpoints, compared AVT03's pharmacokinetics, safety, and tolerability profiles to the originator medicine Prolia in healthy adults. Both, the originator and the biosimilar target the RANK ligand to reduce bone resorption and cancer-induced bone destruction.

AUTOIMMUNE DISEASES

In January, **InflaRx NV** presented initial results of a Phase I dose escalation study with its allosteric C5aR antagonist INF904 designed to treat complement-mediated inflammatory autoimmune conditions. The pharmacokinetic and pharmacodynamic data observed make the immunology specialist optimistic. The selective blocker of the complement system administered over 14 days in a dose range of 30 mg once daily (QD) to 90 mg twice daily (BID) led to a more than 90% inhibition of neutrophil activation induced by complement factor C5a in healthy volunteers. In addition, Inflarx observed concentration-time profiles with target exposures of therapeutic potential and good tolerability of the drug candidate, with no safety signals of concern over the entire dose range. *In vitro* experiments showed INF904 has very low inhibition of the CYP3A4/5 enzymes, which play an important role in the metabolism of a variety of drugs, including glucocorticoids. Based on the results, the company is now aiming for Phase II testing with INF904. ■

The EU Commission strikes again – New patent ban?

INTELLECTUAL PROPERTY In times of the pandemic it was called to ban patents that are related to COVID-19 vaccines, medicaments, and diagnostics and the European Parliament was in favour of it. Now there is a call from the European Parliament to ban all patents on new genomics techniques (NTG) and plants. Quo vadis?

› Dr Ute Kilger, Partner at Boehmert & Boehmert

On February 7, 2024, the Members of the European Parliament (MEPs) adopted, by way of plenary vote, a position supporting a proposal of the Committee on Environment, Public Health and Food Safety (ENVI) to ban patents for all plants obtained by New Genome Techniques (NGT plants), plant material, parts thereof, genetic information and process features they contain. What does this mean?

New Genomic Techniques (NGTs), such as genome editing using CRISPR-Cas, can significantly improve the speed and precision with which new plant varieties are created. In Europe, intellectual property (IP) protection of biotechnological inventions, including NGTs, is regulated through the European Union (EU) Biotechnology Directive 98/44/EC. In addition, breeders can obtain single IP rights on both propagating and harvested materials (i.e., 'Plant Breeders' Rights'), but especially the patenting of harvested materials is heavily debated and controversial.

Back to the future

But – before jumping into the details of the heated discussion let us take a step back to have a look at the full picture. The world is full of legitimate interests that needs to be balanced. There are different stakeholders in a certain ecosystem that have different legitimate positions. There is the legitimate interest of patients to have access to affordable medicines. There is on the other hand the legitimate interest of those who invest into the development of medicines to get some return on their investment once the medicament is marketed. Patents are one tool of those who invest into innovations to secure some return on investment. These different interests need to be balanced.

Dr Ute Kilger,
Partner, Boehmert & Boehmert, Berlin

Populistic voices who pretend to represent the interests of the patients called for a ban of patents to certain medicines, e.g. COVID-19 vaccines or drugs. Their populistic "logic" consists of the assumption that the ban of patents on medicines would "free those medicines" and hence, "everybody" has affordable access thereto. Like most populistic ideas, this falls short. Like most populistic ideas, they are nevertheless liked by people and disturbingly also by politicians. The real world is, however, a bit more complex: No patents on drugs means no investment into new drugs, no new drugs, no access to new drugs for patients as there are none. For those who work in this business this is an easy-to-understand reality. Unfortunately, this reality is mostly unknown to the public as the populistic voices are more popular and politicians tend to follow the easy and populistic route it seems. Furthermore, pharma and patent bashing seems woke, isn't it?

Breeders and inventors

Now, there is a legitimate interest of the breeders and farmers who do not employ NGT not to be unnecessarily bothered by patents. New Genomic Techniques (NGT) can improve the speed and precision with which new plant varieties are created. For breeders not using such techniques, developing new plant varieties is generally an expensive and time-consuming endeavour. The patentability of NGTs raises concerns among breeders and farmers, e.g. regarding the possible monopolisation of traits via the patent system and the possible accidental infringement of patents. Also, many small- and medium-sized breeders fear that it may become impossible to have access to the protected genetic material for breeding on reasonable terms.

On the other hand, companies investing into NGTs have a legitimate interest to protect their innovation and get some return on their investments. Mankind may have a legitimate interest in sustain-

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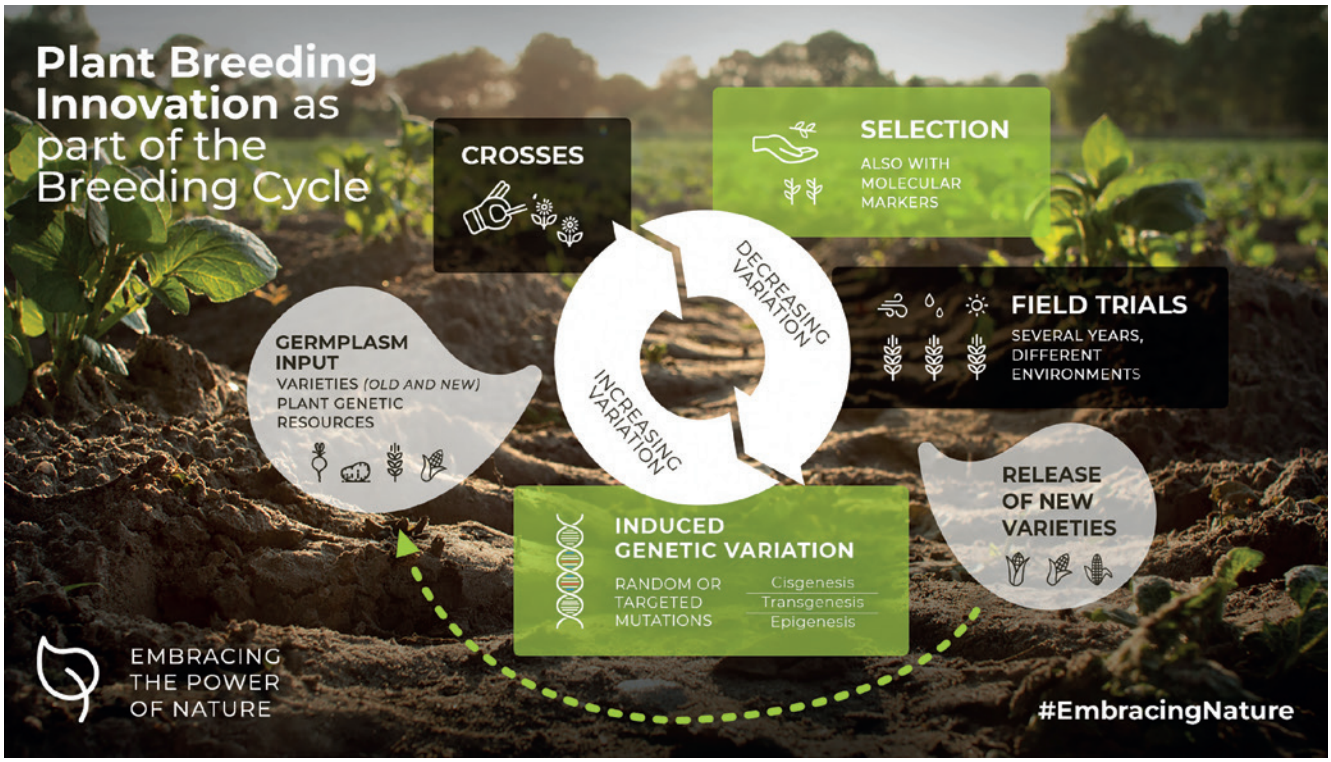

able crop development, environmental safety, and food security through the development of more drought- and/or salt-resilient, disease-resistant, and higher-yielding varieties.

Banning NGT patents?

Will the proposal to ban patents for all plants obtained by NGT provide a balance of all legitimate interests? Certainly not! Instead of balancing these legitimate interests it seems the baby shall be thrown out with the bathwater. The populistic approach to ban patents will not lead to new sustainable crop development, environmental safety, and food security that may be provided by NGT. It will also not lead to investments into NGTs, at least not in Europe. The proposed plant patent ban would put the future of innovation in this area in Europe at risk, and compromise Europe's long-term competitiveness. The proposed ban, therefore, undermines the aims of the original Commission proposal, which was expressly intended to create "an enabling environment for research and innovation" in the NGT plant sector. Breeders fear that they do not have access to all genetic material for further breeding due to the protection of these materials by patents. Breeders are concerned to infringe an existing NGT-plant-related patent in case they develop plants with the same features as the patented ones without using the patented NGT. There are concerns whether breeders may obtain affordable licenses if needed. Quite often the risk of unintentional patent infringement is debated that may occur due to naturally occurring cross-pollination between fields. For breeders it is often non-transparent what patents exist at all.

Risk of patent infringement

The legitimate interests of the farmers and breeders can and shall be addressed without compromising Europe's competitiveness. Research exemptions, limited breeders exemption, patent pools, in certain cases compulsory licenses may all be tools to address the interests of farmers and breeders. Certainly, there are open issues that need to be addressed. This should, however, be done by involving all stake holders in this area. And it should be done by keeping all interests in mind: the interests of the farmers and breeders, the interests of the many European-based start-ups, SMEs, and research organisations active in the plant- and agricultural-biotechnology fields, the interests of Europe and the European community to have a competitive Europe that is not compromised by populistic politics and a Europe that can compete with China and the USA.

Thus, the impact study as requested by MEPs should also engage with representatives from the full breadth of (industry) stakeholders, including the many European-based start-ups, SMEs, and research organisations in the fields.

New monopolies?

It is an unfortunate misconception that patents are merely used by large multinationals to create monopolies to the detriment of SMEs and the public. This is untrue. In particular SMEs and research organiszations must rely on patent protection to compete with the established players. And it is in the interest of the public that new technologies come to the market. Moreover, it is in the interest of the European community that Europe is strong and competitive – which would be put at risk by any new patent ban. ■

Picture: © Euroseeds

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BIOENGINEERING Whether therapeutics, novel food or sustainable bioproduction: the UK is leading the way with a £2bn bioengineering initiative over ten years that in its first draft was 90% biomedical, but has been revised after the US bioeconomy strategy came out.

Launched last December at SynbiTECH in London, the new "National Vision for Engineering Biology" lays out the government's strategy to seize engineering biology and scale-up of production processes, now in medicine, food processing and agricuture as well as sustainable fuel production. The £2bn funding over the next decade that has not yet been specified together with the launch of a new Engineering Biology Steering Group is hoped to bolster economic growth in the UK and creating higher-paying jobs and opportunities across various industries throughout the country.

Skilled staff needed

As more than a third of CDMOs are struggling to keep skilled technical and production staff, attractive framework conditions created through the UK's initiative are set to make up for lost ground. According to BioPlan Associates' 20th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production in 2023, the inability to hire new and retain experienced technical and production staff will be a major constraint on biopharmaceutical manufacturing capacity. Almost 32% of all respondents identified the inability to hire new, experienced scientific staff as a factor creating capacity constraints over the next five years, up from 19.4% in 2018, confirming that this bottleneck has grown steadily. Both, upstream/downstream process development staff was hard to find, said 42% of respondents.

Providing infrastructure

Overall demand for bioprocess supplies remains strong, and growth is anticipated in both established and emerging segments with new therapeutics such as ADCs and ATMPs on the horizon. However, in contrast to recent years in which capacity constrains dominated the survey, staffing problems are relatively new to the sector.

The UK had already created a framework to attract qualified staff establishing additional gene and cell therapy hubs besides the CGT Catapult, adressing process intensification in GMP viral vector manufacturing. With this initiative, the UK is also responding to the fact that China has taken the lead in clinical trials for ATMPs over the USA and Europe (see graphics p. 58).

Global CDMOs such as Lonza AG have already reacted. At the end of January, the UK arm of Lonza AG struck a deal with Oxford Nanopore Technologies plc to develop and market a sequencing test to assess multiple critical quality attributes of mRNA products. ■

A novel BPM system

PROCESS TRANSFER The biotech and pharma branch is growing steadily. Many companies have full order books for the next few years and expect growth. This is the basis for new investments in assets and infrastructure. These growing structures often expose vulnerabilities and challenges for the business. Therefore, companies need to increase the stability and efficiency of their processes.

› Tobias Meder, Business Process Expert at Richter-Helm BioLogics GmbH & Co.KG

Richter-Helm is one of the companies currently expanding to serve the needs of the biotech and pharma market. There will be a significant increase in manufacturing capacity at the company´s production site in Bovenau. The new building will be one of the most modern facilities in the world and perfectly meets the company's high standards in GMP-compliant CDMO business. It will be ready for operation this year. The current challenge is to transfer the well working processes to the new facility. Thereby, Richter-Helm is continuously improving and standardising the processes of the entire company. Richter-Helm will be able to differentiate itself from the competition in the CDMO business and respond more flexibly to the needs of its customers.

Business Process Management (BPM) is the structured approach to achieving this goal by making activities, responsibilities and interfaces within an organisation transparent. Implementation begins with the documentation of business processes. This is the basis for later analysis and optimisation. It is recommended to start with a top-down definition of the most important processes. The result

is the process landscape which represents the main processes. The next step is the detailing. Therefore, the worldwide standard BPMN 2.0 (Business Process Modelling Notation) which is used by most of the companies can be used. The introduction of a BPM software is recommended to simplify the modelling.

During the modelling, companies with several locations often face the problem that their processes work differently. Different executions of the same process can lead to variations in the quality of the products delivered to the customer. This may affect the reputation of the company and the customer satisfaction. So, the first step should be the standardisation to increase the efficiency of the process and the quality of the output. In this way, sites can learn from each other and adopt best practice. At first glance, this may seem like a simple quick win, but it requires very good change management to get everyone on board. It is therefore important to involve representatives from affected sites as early as possible. Otherwise, the standardisation will only be valid on paper, but won't be implemented. It is also important not to force standardisation on every process. The implementation of BPM is an ongoing process to continuously improve the maturity of the organisation. The North Star is the achievement of the level "Continuous Improvement". This level is never finished, because process improvement doesn't stop. It is always assumed that the current process is the worst process and must be improved. ■

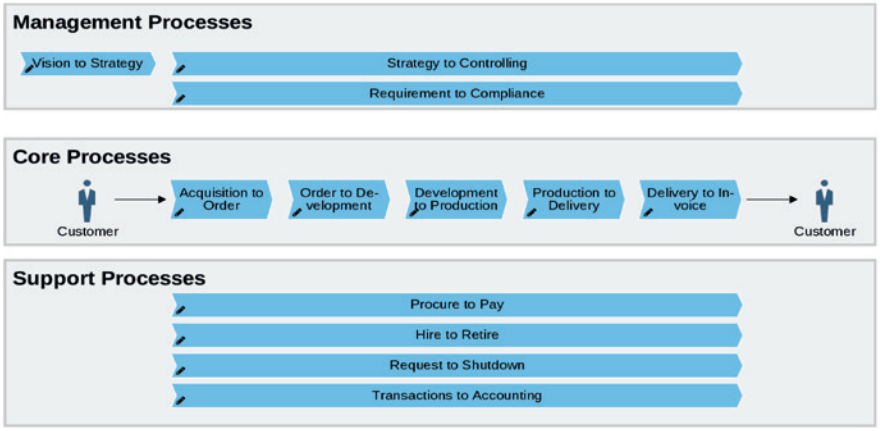


Figure 1: Example of a process landscape

Picture: © Richter-Helm Biologics GmbH & Co.KG

Experts in microbial technology

BIOMANUFACTURING The world of microbial product manufacturing is a complex landscape, driven by a diverse range of molecule formats and manufacturing processes. At the forefront of this specialty market is Boehringer Ingelheim Vienna, one global leader in biopharmaceutical development and manufacturing.

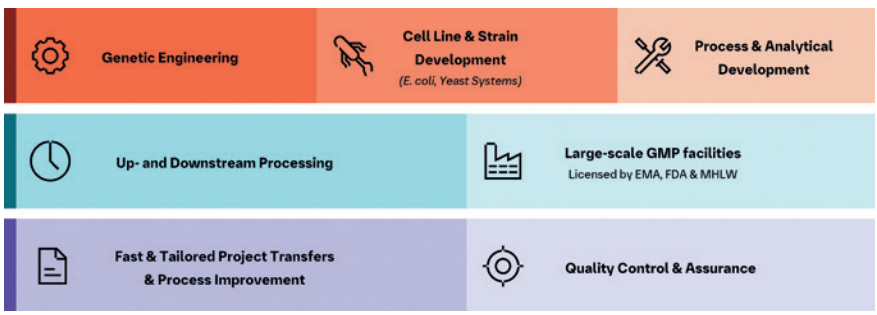
With over 40 years of experience, Boehringer Ingelheim Vienna has developed and manufactured more than 150 molecules using mainly *E. coli* and yeast systems. These molecules range from recombinant proteins and peptides to antibody-like molecules, sub-unit vaccines, virus-like particles, and plasmid DNA. This extensive experience, combined with their broad commercial expertise and development capabilities, allows them to offer a comprehensive value chain from early-stage development to commercial launch.

Boehringer Ingelheim Vienna operates three facilities, offering flexibility with cGMP scales ranging from 300 L to 6,000 L. These multi-licensed facilities, designed for high cell density processes, have a strong manufacturing track record with 19 commercial products for global markets.

Their downstream capabilities handle a great variety of molecule formats mainly manufactured in *E. coli* and yeast systems. They are built on their long standing experience in protein refolding as well as soluble expression and purification at large scale, also including special techniques for difficult to manufacture proteins. To cater to these requirements facilities allow for handling organic solvents, HPLC chromatography is also available on large scale via commercial scale columns up to 1.8 m diameter and lyophilisation of bulk material is an established process step. In addition, chemical modification strategies can be applied to prolong the protein´s half-life. Among the approaches used by the company are strategies to increase size by the chemical coupling of polymers (PEGylation or HESylation) and the use of FcRn mediated recycling, such as fusion to human serum albumin (HSA) or albumin-binding moieties. Generally speaking, microbial expression systems are most suitable for synthesis of smaller and non-glycosylated proteins, whereas larger proteins like monoclonal antibodies require mammalian cell culture to be expressed. Due to the short doubling time (minutes instead of hours) microorganisms-based upstream processes are significantly (up to 30-fold) shorter than mammalian processes and yield high product titers up to 20 g/L fermentation broth.

Besides recombinant proteins, plasmid DNA for gene therapy and viral vectors can also be manufactured in *E. coli*. Boehringer Ingelheim has developed and continually fine-tuned a manufacturing process specifically designed to yield high-quality plasmid DNA. This process leverages the potential of scientific breakthroughs for patients.

A wide variety of molecule formats can be produced via fast cultivation in microbial systems, which present their own challenges. They require tailor-made processes, which Boehringer Ingelheim Vienna addresses with platform-like technology modules and a versatile toolbox to serve individual needs.



Our broad commercial expertise and development capabilities cover the whole value chain.

Microbial Process Development

Microbial systems, like *Escherichia coli* and *Komagataella phaffii*, are used to produce various proteins. The proteins can accumulate in different forms, requiring specific expression, purification, and sometimes refolding processes to reveal the proteins native and active state. These steps can be time-consuming, potentially limit throughput and may result in product losses. Re-

Picture: © Boehringer

gardless of the expression strategy, the need for a custom purification process adds complexity to process development and manufacturing in multi-product facilities. Technologies that simplify processes by introducing platform-like steps are beneficial for streamlining development and manufacturing, and for increasing productivity.

Fusion protein technologies, for instance, are extensively utilised to enable soluble expression and subsequent affinity purification in *E. coli* . However, they present several challenges, such as a reduction in product yield due to the relatively high molecular masses of tags or, more critically for biopharmaceutical applications, conformational changes that could compromise the efficacy and safety of the therapeutic protein. Boehringer Ingelheim has explored an N-terminal fusion tag, demonstrating its applicability across a broad range of molecules.

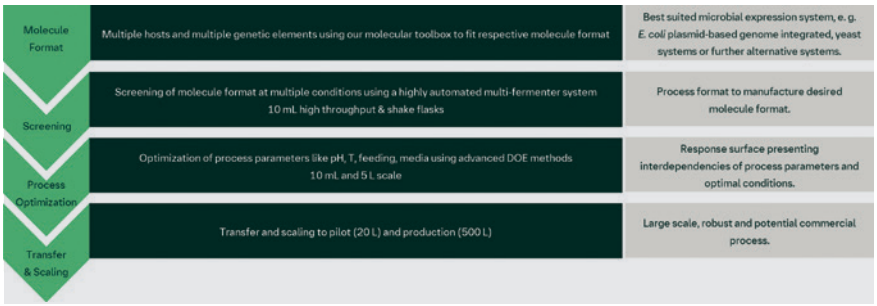
The so-called CASPON™ (CASPase-based fusiON) system, in particular, features a peptide fused to the N-terminus of the protein of interest and a highly specific protease to remove the tag post-purification, thereby preserving the authentic N-terminus of the target protein. Among other benefits, the tag incorporates a histidine stretch for platform affinity purification.

This exemplifies how platform-like techniques can be effectively used to mimic platform processes that are well-established for purification in cell culture manufacturing.

After defining the molecule format, a number of genetic tools can be utiliszed to boost the productivity of microbial systems. Boehringer Ingelheim has created a comprehensive toolbox, including strains, plasmids, promotors, leader sequences, and helper factors, which have been effectively used to increase soluble expression in *E. coli* by over 25 times.

The full potential of this multifaceted set of tools can only be harnessed with a predictive screening system. However, conventional screening systems using deep well plates or shake flask cultures often fail to accurately predict results for large scale high cell density fermentations, particularly for *E. coli*. To resolve this, Boehringer Ingelheim has engineered a miniaturiszed fermentation system on a milliliter scale that facilitates predictive screening of different constructs in an automated, parallel fashion. This system, coupled with miniaturised, parallelised, and automated screening systems for purification and analytics, paves the way for high throughput process development.

A predictive system is crucial for selecting the most productive strains and for the development of robust processes, which can then be scaled up and transferred. Boehringer Ingelheim employs tools such as computational fluidic dynamics (CFD) to characterise vessels of different scales and adjust small scale equipment to closely mimic the large-scale production environment.



Our general approach from lab to commercial scale for recombinant protein manufacturing.

Digital Tools for process boost

Digital tools hold considerable potential to further enhance the development and manufacturing of biopharmaceuticals. The process of developing a biopharmaceutical production process is typically sequential, and optimising each individual unit operation can be quite laborious. In this process, the conditions deemed optimal for one step serve as the basis for the next. However, this approach does not take into account potential interactions between a priori distant process steps, and therefore, cannot ensure optimal overall process performance. Data-driven integrated process models that employ machine learning techniques and genetic algorithms are powerful tools for simulating and optimising manufacturing processes. The company's SMART Process Design software platform predicts how to adjust process parameters for optimal output. The result of this approach is a manufacturing process that provides efficiency, quality, and speed for the desired molecules, applicable to both clinical development and market supplies.

Summary

Microbial Manufacturing Technologies and Boehringer Ingelheim's capabilities in this field offer a powerful means to produce a diverse array of products. Platform-like technologies for non-platform molecules can significantly enhance the use of microbial hosts. Digital tools for characterisation and prediction minimise the needs for wet-lab experiments and contribute significantly to the development of robust, well-understood processes. This guarantees a speed-up of time to clinic and market, ensuring patients' access to innovative medicines.

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Richter-Helm – how CDMOs become strong partners

CDMO Professionalism and quality are always at the forefront along the whole value chain: from gene to product. To pro-actively meet the evolving demand of the market to produce new assets Richter-Helm significantly increased its manufacturing capacities for biopharmaceutical products at its production site in Bovenau, Germany.

› Dr. Thilo Kamphausen, Director of Business Development; Dr. Kai Pohlmeyer, Managing Director, Richter-Helm BioLogics GmbH & Co. KG

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Within the highly competitive CDMO market Richter-Helm established itself as first in class service provider and partner. Decades of experience, highly motivated employees and the trustful and strong ongoing partnership to its clients continues to consolidate this position. Known to be a highly flexible partner, Richter-Helm further expanded its production, development and analytical capacities in line with customer requirements.

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GMP PharmaCongress 2024 – vaccines, ATMP and more

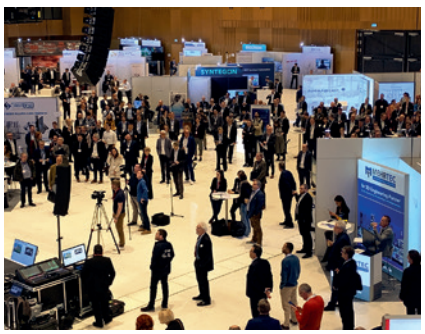
MEETING Pandemic preparedness, new vaccines and gene therapies – together with the classic aseptic manufacturing topics the PharmaCongress 2024 offers a comprehensive programme.

› Axel H. Schroeder, Operations Director, Concept Heidelberg

In addition to classic aseptic manufacturing topics, the international GMP PharmaCongress and GMP PharmaTechnica Expo 2024 in Wiesbaden, Germany, will address global challenges with modern vaccines and novel drugs based on cell and gene therapies. The event thus offers a comprehensive programme for experts from pharmaceutical manufacturing, technology and quality assurance from industry, labs and authorities, as well as a platform for the direct exchange of knowledge and experience.

One of the major challenges in today's era of globalisation, rapid travel and global mobility is to achieve appropriate preparation for pandemics. This requires, among other things, the development of modern vaccines, which must also fulfil a number of requirements:

- Safety: guaranteed by extensive clinical studies and post-market surveillance
- Efficacy: High level of protection against the respective disease, also extensively tested in clinical studies
- Long-term protection: Longest possible protection
- Stability and storage: High stability under different environmental conditions with worldwide use
- Adaptability: Flexible adaptation of the vaccine to new variants of the pathogen
- Production and availability: Rapid production, prepared distribution channels
- Public acceptance: Clear communication of the advantages, risks and benefits



- Ethics and accountability: Compliance with ethical standards during development and production

However, other aspects also play a role in preparing for possible pandemics, such as early warning systems, monitoring and response for early detection (AI, big data analysis and telemedicine) with international cooperation, increased research and development for modern vaccines, antiviral drugs and new therapies (platform technologies), building up stocks and emergency reserves, strengthening healthcare systems and transparent communication and education.

One step in this direction is CEPI, the Coalition for Epidemic Preparedness Innovations. The CEPI's Centralised Laboratory Network is the largest global group dedicated to standardising the assessment of vaccines being developed against some of the world's most deadly outbreak diseases. Harmonising readouts on vaccine performance in a collaborative approach can expedite the development and regulatory approval of vaccines to enable faster responses to future emerging threats. This supports the 100 Days Mission, a goal, spearheaded by CEPI and embraced by the G7 and G20, to develop vaccines within 100 days of identification of a viral threat.

The PharmaCongress 2024 is also taking these requirements and developments into account, firstly with a new conference track on vaccines and secondly for the opening of the congress with a key note on the CEPI project, which now involves 40 countries and various organisations.

PharmaCongress 2024 offers a total of 11 conference tracks ranging from aseptic manufacturing to challenges in ATMPs and sustainability in manufacturing with modern technologies. The parallel PharmaTechnica Expo with 115 exhibitors and almost 20 live demos will also provide information on technical innovations and modern services in the GMP and GDP environment. ■

Axel H. Schroeder

› QUICK FACTS

GMP PharmaCongress & GMP PharmaTechnica
19/20 March 2024
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Wiesbaden, Germany
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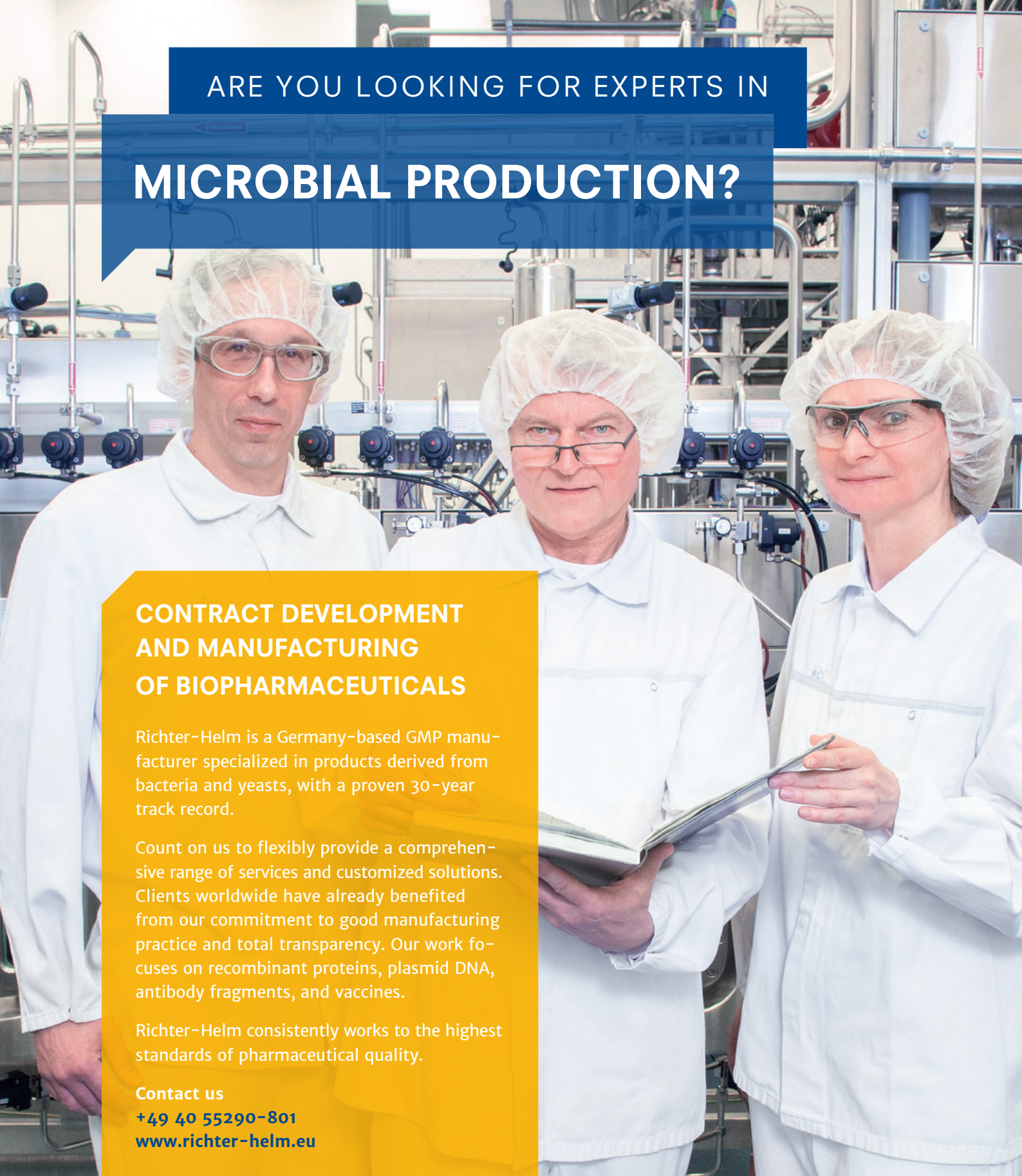

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Biology as Software

SYNTHETIC BIOLOGY At a recent event researcher and founder of Bit.bio, Prof. Mark Kotter, Babraham Research Campus in Cambridge/UK, was asked what healthcare looks like in 2050. He gave a twofold answer, that it will be driven by data, but also will be personalised. Mark Kotter elaborates here in more detail what is needed to unlock a healthcare of tomorrow.

As technology develops further our lives will continue to be filled with wearables — in our clothes, wristbands or potentially something that's implanted under the skin. These devices will gather behavioural and biochemical data 24/7, constantly monitoring our health, and allow us to detect diseases very early by spotting changes in patterns in the collected data. As a consequence, the spectrum of diseases that we need to target will change. Early detection may improve the efficacy of current treatments. In addition, the exponentially increasing biomedical knowledge will provide endless opportunities to develop new and more potent medicines.

A key to unlocking it lies in having access to human cells, the fundamental building blocks of life. In 2050, cell therapies will permanently rejuvenate our immune systems, preventing cancer and boosting our resistance to infectious disease. Lost organs will be replaced by new ones, 3D printed from individual cells. We will have medicines that are highly personalised and matched to our specific needs. Conditions that are now thought to be untreatable, will have new cures. Regenerative medicine will have become a reality.

Problems to overcome

A lot needs to be done before we get there. One significant bottleneck to developing these new medicines is a reliable, consistent supply of human cells. This is critical for translating scientific findings into therapies. A reliable and scalable source of human cells has the potential to transform research and drug development in three ways:

Mark Kotter, Cambridge

› Setting standards

Reliable 'off the shelf' human cells are able to address the well documented reproducibility crisis in science. If researchers had a consistent source of human cells to benchmark their experiments this would enable greater comparability.

› Medical avatars

Human biology is unique. Using human cells to investigate basic research questions provides the best starting point for biomedical research. Many conditions are specific to humans. For example, mice don't get Alzheimer's, hence it has been tremendously difficult to translate research findings made in mice into clinical therapies.

At the preclinical stage of drug development, before a single person is dosed with an investigational drug, the use of human cell models will enable us to preempt data that today requires large scale multi-centre studies involving hundreds or thousands of patients.

Medical avatars are needed for better clinical translation and personal simulation. Such avatars are created with, for example, human brain cells from different individuals, will enable us to simulate cohort studies without having to dose a single human being. This will increase confidence in drug candidates and at the same time help us to identify the patient groups that are most likely to respond. In addition, toxicology panels consisting of liver cells will enable us to quickly work out whether a drug is harmful and in particular the groups of individuals that are most likely affected based on their personal genetic makeup. And these avatars can also be personalised with our own cells and used to predict our own response to treatments.

› A new class of (cell) therapies

We are at the beginning of the third wave of medicines: cells themselves being used as drugs that are intelligent and react to their environment. These therapies are starting to emerge and the early results are astonishing: patients who suffer from untreatable blood cancers are cured by having their T Cells reengineered with chimeric antigen receptors (CARs) to attack their cancer. The next generation of cell therapies will be precise, highly consistent, and scalable; and it will extent the use of cells to tackle diabetes, Parkinson's, genetic diseases, and many other conditions.

Revolution in drugdevelopment

With these tectonic shifts occurring all at the same time, we are in the middle

Picture: © Bit.bio

of a revolution in how we develop new drugs. This will lead to more precise and personalised medicines. Naturally this will also lead to an expansion of all medical technologies, including cell therapies at scale.

Reimagine biology!

So why has this not happened already? Because today, getting hold of human cells is difficult — we rely on donors where the variability is high and the bottleneck is finding donors in the first place. Some cells are impossible to source — for example, I don't know anyone who would like to donate their brain cells …

A long hailed alternative to harvesting cells from human individuals are pluripotent stem cells. Their promise was that they can be used to create any cell type via a process called directed differentiation, which mimics embryonic development. However, after nearly thirty years of research, we have learned how difficult this is. Only a handful of cell products have been created using this process and these are not widely used.

The third option is based on synthetic biology. This is what bit.bio is working on. We reprogram cells with a new identity to manufacture cells at scale.

To do this, we have to reimagine biolog and take a software approach where the identity of a cell is something we can program.

Biology is our software

For this purpose let's look at a cell as if it were a piece of hardware, a biological computer. The nucleus contains the DNA. This is the hard drive of a cell (mainly consisting of ROM). Here all the genetic programs of a cell (organised in gene regulatory networks, GRNs) are stored; together they form LifeOS(TM), their operating system. At any particular moment in time, only a subset of genes are active and transcribed into RNA. Together, DNA and RNA form the information layer, which is translated into the physical and structural components of a cell that define its function and identity.

By changing the active programs (GRNs), it is possible to change the identity of the cell. This can be achieved by activating the appropriate transcription factors, a specific subset of genes, which act like 'coding' words of a programming language, controlling the activity of the genetic programs.

'Programming' living cells is not new. This synthetic biology approach has been applied to bacteria, yeast and other simple organisms to create sophisticated medicines, such as antibodies, and more recently materials for industrial production. But the human cell is far more complex and more difficult to control.

The first evidence that human cells can be reprogrammed dates back to the 1980s when Harold Weintraub's team identified a new gene, encoding a transcription factor he called MyoD. When they introduced MyoD into other cells they turned into muscle cells. His findings challenged many existing dogmas about what constitutes cell identity. Unfortunately, his knowledge was lost for nearly 30 years, until 2006 when Shinya Yamanaka developed a reprogramming protocol for turning skin cells back into pluripotent stem cells.

Yamanaka's discovery will turn out to be one of the most transformative scientific discoveries in this century. Now every individual can have their own personal rejuvenated stem cells (or induced pluripotent stem cells, iPSCs), generated from a simple blood draw. These findings have inspired a number of talented scientists, to explore whether this concept of cell reprogramming could be applied to other cell types. Since then the field has taken off and many more cell types have been reprogrammed.

Finding the start button

One of the challenges that limits successful reprogramming of cells is a process called gene silencing. The cells recognise that the transcription factors activated as part of the reprogramming process are at odds with their current state and switch them off before they convert into the new cell type. This is where the technology developed in my lab, that is now the foundation of bit.bio, provides a solution. Opti-ox(TM) is a control system that is inserted into specific locations in the DNA called genomic safe harbour sites. It consists of the transcription factors combination required for reprogramming into a particular cell type and a genetic activation switch.

Genomic safe harbour sites are unique locations in the genome that allow engineering cells without interfering with their function; they are also less prone to gene silencing than other areas of DNA. Using opti-ox, it is possible to deterministically reprogram pluripotent stem cells (iPSCs) into the desired target cell type. So far we have been able to generate brain cells, muscle and fat cells, various immune cells, liver cells, and so on in a highly reproducible and scalable manner.

On the eve of construction

These findings break several scientific dogmas, such as the need for epigenetic remodelling that forms part of the differentiation process, and the idea that biology is a 'fuzzy science'. opti-ox indicates that in order to deterministically reprogram a cell, it is necessary and sufficient to control the expression of the reprogramming factors.

With opti-ox it is possible to instruct cells to execute a new program, without escape, as if they were a piece of hardware and turn them into a mature cell type. This determinism and granular control of cellular states driven by transcription factor combinations transitions biology into engineering.

Democratise cell therapy

The implications are significant: we may finally be able to unlock the promise of stem cells and regenerative medicine for a medicine of tomorrow. And we can democratise stem cell technology in greater width. We are close to designing health not just to heal. ■

Well-intentioned, badly done: The digital EU reporting system for clinical trials CTIS, managed by the EMA, allows a reporting EU Member State to register a multi-centre trial in any number of EU Member States at the same time with a single notification. The idea is to achieve better coordination through better communication. Trials registered under the old EudraCT system must be switched to CTIS by 31 January (2025) at the latest.

CTIS: Clinical trials in slowdown

INFORMATION SYSTEMS Even before its launch last year, drug developers, CROs, ethics committees and clinicians began criticising the technical implementation of the EU study portal CTIS. Though the most serious programming errors have now been eliminated by the EU authority EMA, the goal of simplifying the registration of multi-centre trials and making the bloc more attractive to trial sponsors was clearly missed. What are the consequences for Europe?

Clinical trials that are carried out in a timely, compliant and successful manner can shorten time to market, and thus significantly increase sales of drugs within patent terms. It's therefore no surprise that study sponsors look for locations that are able that help get their medical innovations to patients as quickly as possible. Competition between potential sites fuels the global race to market, so it boils down to hard cash. According to Markets & Markets, the global clinical trials market size stood at US$54.24bn in 2022, and is projected to grow by 6.9% annually to US$92.45bn by 2030.

In order to improve the position of the EU against rising star China and the undisputed top dog – the US – in terms of studies carried out (see Fig. 1, p. 56), the European Commission developed the idea for a digital portal back in 2012 as part of EU Regulation 536/2014.

"The idea behind the adoption of EU Regulation 536/2014 was a good one," stresses Martin Krauss, Managing Director of FGK Clinical Research GmbH and Chairman of the Board of BVMA e.V., which represents the interests of Germany's contract research organisations (CROs). "The digital, simultaneous application for the European Economic Area EEA (30 countries) was meant to harmonise the previously time-consuming sequential application for clinical trials, and enable the start of trials with an identical protocol in each participating country at the same time," he explains, "which is particularly important for large multi-centre pivotal trials."

> To put it mildly, the fact that CTIS is not working so well makes Europe unattractive to study sponsors – we have to realise that.
>
> Biopharma stakeholder, confidentially

Accordingly, Article 80 of the law states: "The portal must be kept up-to-date with the latest technology so that no unnecessary workload is created." On paper at least, the concept sounded convincing. Application via CTIS would be sufficient for all participating countries, and significantly speed up recruitment. In reality though, even after a 12 month technical check before the new system became mandatory – with a two-year transition period for ongoing studies registered under the old EudraCT system – it didn't work right. Files couldn't be uploaded, as well as data on members of the ethics committee. The maximum data volume for the documents required in the application was also too small, among other issues. As the response deadlines for enquiries to the applicant were often tight and fixed to the minute, costly new applications had to be submitted if initial uploads to the portal were unsuccessful.

Well-meant, but disappointing

So even before CTIS went into effect on 31 January 2023, critique about the new EU study portal had grown loud. "It's sad but true that, according to experts, it wasn't state-of-the-art when it was launched," according to Dr Thorsten Ruppert, Senior Manager Research, Development, Innovation from German pharmaceutical association vfa. He told European Biotechnology that "the implementation of the good idea is disastrous" – an assertion stressed by associations and chief investigators.

In the months since the launch, the European Medicine Agency (EMA), which administers CTIS and is responsible for its maintenance, has made a huge effort to rectify the most serious errors. No easy task on a project patched together by three tenders over nine years. However, completing applications in the system is still very time-consuming, says Krauss. Some in the European CRO umbrella organisation

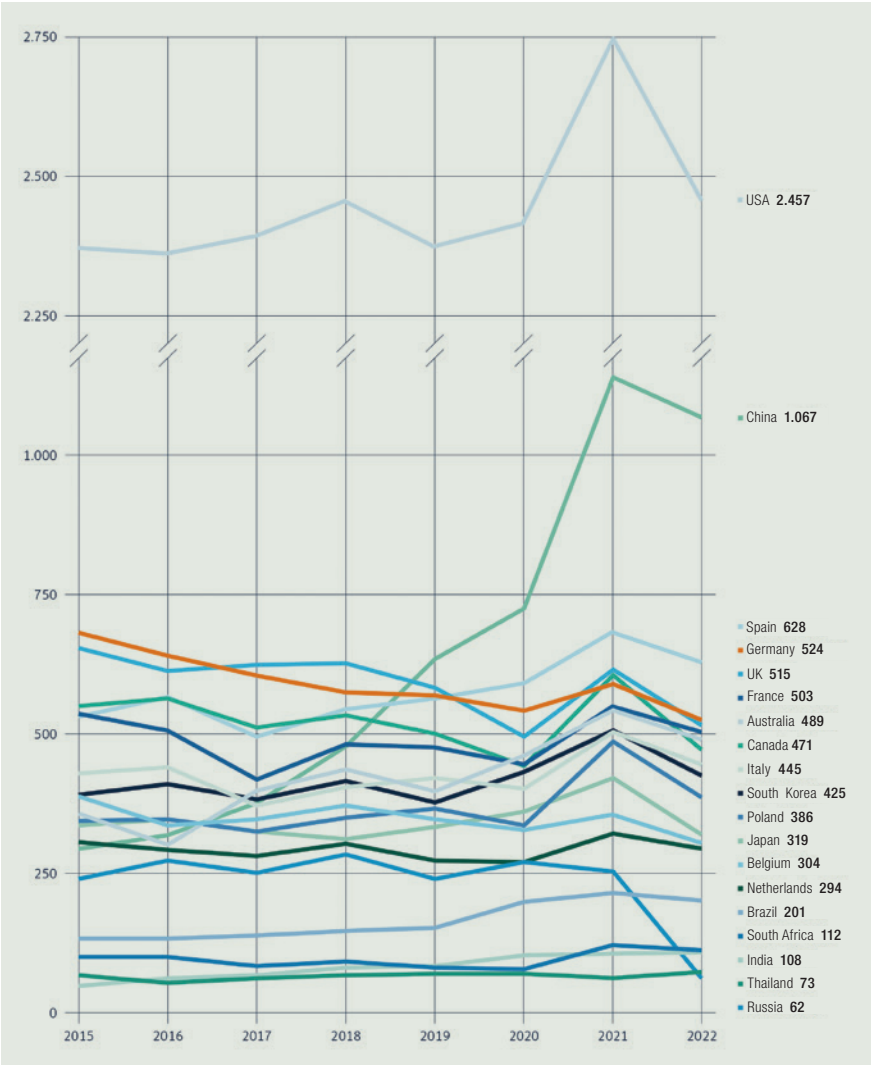

Figure 1: Ranking the number of clinical trials per country between 2016-2022

Country	Rank/2016	Rank/2018	Rank/2020	Rank/2021	Rank/2022
USA	1 / 2,362	1 /2,456	1 / 2,416	1 / 2,749	1 / 2,457
Germany	2 / 642	3 / 575	4 / 542	6 / 589	4 / 524
UK	3 / 614	2/627	5 / 496	4 / 615	5 / 515
Spain	4 / 566	4 / 545	3 / 591	3 / 682	3 / 628
Canada	5 / 565	5 / 534	8 / 444	5 / 605	8 / 471
France	6 / 505	6/ 482	7 / 446	7 / 549	6/ 503
Italy	7 / 441	10 /404	10 / 403	10 / 504	9 / 445
South Korea	8 / 409	9/416	9 / 431	9 / 506	10/ 425
Japan	9 / 348	13 / 312	11 / 360	12 / 420	12 /319
Poland	10 / 347	12 / 349	12 / 337	11 / 486	11/ 386
Belgium	11 / 337	10/ 404	13 / 328	13 / 356	13 /304
China	12 / 320	7 / 480	2 / 725	2 / 1,139	2 / 1,067
Australia	13 / 301	8 /436	6 / 479	8 / 542	7 / 489
Netherlands	14 / 291	14 /303	14 /271	14 / 321	14 / 294

EUCROF have called it “sometimes very frustrating”.

Not a good selling point

“Even before the launch of CTIS, Europe’s image had been tarnished,” Krauss believes. “The entire industry knew that we were working with a technical system that was not ready to simplify the application process in Europe. It added unnecessary complexity instead of providing a user-friendly state-of-the-art portal. And that doesn’t just affect clinical research, but also the production of the clinical lots and pharmaceuticals by contract manufacturers (CDMOs), which EU decisionmakers want to bring back to Europe in the wake of the pandemic.” A study by the globally active consultancy Charles River Associates reported a migration of 6% of EU studies to Asia in 2020, many to China. In January 2023, German flagship company BioNTech SE (Mainz) announced it would conduct its studies on mRNA cancer vaccines in the UK due to the excellent framework conditions there. According to Ruppert, although the UK saw a slump in the number of clinical trials due to staff shortages and Brexit (see Fig. 1), the country “is on the path to overcoming the problems and is expected to return to the top group of study locations.”

According to Krauss, the competent authority MHRA faced a “catastrophe” as it was unable to authorise a single newly submitted study for almost six months due to massive staffing problems. That situation threw an unsightly dip in the otherwise flawless slope of clinical trials carried out. “A huge campaign was then launched in collaboration with industry to hire former MHRA employees, some of whom had moved to industry – a spirit that we would like to see in the EU,” says Krauss. They are now able to work again, and are increasingly cooperating with Australia and New Zealand, which are also marketing themselves proactively as study locations for pharma.

Now that the EMA has got CTIS up and running, the next challenge for

Picture: Vfa, Source: clinicaltrials.gov

Not a positive signal for EU attractiveness

VALENTIN PLOUCHARD *Healthcare Regulatory Affairs Manager – EuropaBio: Since going live two years ago, the practical implementation of the Clinical Trials Information System is not yet delivering the seamless management of clinical trials by sponsors in the EU. However, we must acknowledge remarkable efforts from the EMA to ensure incremental improvements of the system. It is not so much CTIS per se that poses an impediment to clinical trials in the EU, but peripheral issues linked to the more general implementation of the Clinical Trials Regulation. Two issues must be singled out concerning the transition from the Clinical Trials Directive and new rules on transparency of information relating to clinical trials. For the former, many clinical trials remain to be transitioned under the new rules and are facing delays in approval of transitional application at the Member State level. As regards new transparency rules that are to enter into force in 2024, and despite an enhanced dialogue between the EMA and industry stakeholders, more open rules on the disclosure of commercially confidential information might be seen by sponsors and small innovators as a negative signal for the attractiveness of conducting clinical trials in the EU. This situation runs the risk of having fewer clinical trials in the European Union, and in turn risking that breakthrough innovations are not adapted to the needs of European patients and also depriving them of early access to potentially life-saving medicinal products and innovative therapies.* ■

Picture: © EuropaBio

sponsors lies ahead: the transition of ongoing studies approved under the old EudraCT system to CTIS by 31 January 2025 at the latest. According to an EFPIA survey that 28 corporate members responded to, these will have to transfer 1,200-1,300 studies to the new system. "If you extrapolate that, you might come up with 2,000-2,500 studies that need to be converted," says Ruppert, who expects an application backlog at the EMA by this summer at the latest.

Transition to the new system

Apparently including the CROs, which carry out 60% of clinical trials worldwide, Krauss speaks of 2,000-4,000 trials, and doesn't have high expectations for Europe as a trial location. "There are major concerns that the EMA can work through this due to capacity limits. Thus, there are a number of global sponsors who will definitely not go along with the transition. This means that they will finalise their ongoing studies in Europe before the transition deadline and then recruit the missing subjects to prove statistical significance at locations like the USA or Asia." Another problem is that confidential data has been inadvertently leaked by CTIS. Transparency guidelines will be changed on April 1st.

Ruppert, however, does not believe there will be a mass exodus, and although the EU associations EFPIA and EuropaBio do not seem satisfied with CTIS, they are more optimistic about the future (see commentary above). According to an EFPIA spokesperson, "the collaborative assessment and centralised IT infrastructure provided for in the EU Clinical Trials Regulation (CTR) promises great potential to streamline and simplify the conduct of clinical trials in the EU. Unfortunately, to date, this potential has not yet been fully realised as a result of the complexity and instability of the clinical trial information system (CTIS) and a lack of alignment regarding Member State requirements for the assessment of clinical trial applications. EFPIA remains optimistic that with proper and pragmatic implementation, the EU CTR, underpinned by a functioning and flexible CTIS, will act as an enabler for multinational clinical trials in the EU."
"There are definitely some companies that are currently accelerating some of their trials to finish them before January 31, 2025 so that they avoid the need to transition them (to CTIS/EU-CTR)," Ruppert told European Biotechnology. "However, we don't have a crystal ball and we don't know how many studies will potentially be carried on abroad. Globally active sponsors can recruit trial participants worldwide to bring up the necessary number of subjects as long as this does not disturb the demanded ethnic mix. If sponsors can recruit in other countries where they can conduct their clinical trials quicker, they might do it. An application in CTIS may require more time, i.e. personnel, than an application in the old EudraCT system," he added. "On the other hand, Europe is an important pharma market that, depending on the EU member state, offers a more or less excellent infrastructure and high patient diversity."

Of course, Europe is in competition with trial locations that also utilise completely different legal options to proactively attract pharmaceutical sponsors. Australia, for example, provides tax credits on clinical trials. In the forward-looking field of cell and gene therapies, what less competitivity could mean for Europe as a centre of innovation is already growing apparent. According to a survey conducted by the Alliance for Regenerative Medicine (ARM), China

What EU member states can do

SPAIN'S CLINICAL TRIAL LANDSCAPE

Within the past decade, Spain has developed into a top player in the European clinical trial network. In contrast to Germany, which is only now making the authorisation and conduct of clinical trials less bureaucratic and burdensome with a "pharmaceutical strategy" and new regulations (thus making it fit for CTIS), Spain was the first EU member state to do this back in 2015 – with a royal decree on the regulation of clinical drug trials. Today, Spain is the European champion in terms of the number of clinical trials conducted by pharmaceutical sponsors (86%), while Germany fell from second place in 2016 to sixth by January 2021. Unlike in Germany, Spain established a centralised, efficient ethics committee for clinical trials (CEIm) in 2016, which cooperates with the Spanish Agency for Medicines and Medical Devices (AEMPS), as well as a register for clinical trials (REec). According to it, Spain has climbed the ranks among European countries with the best conditions for the development of clinical trials. One out of three clinical trials carried out in Europe already has Spanish participation. ■

has already taken the lead from the US in the field of ATMPs and left Europe behind (see Fig. 2).

However, the effects CTIS will have on the number of trials conducted in Europe is difficult to measure. "Based on the fluctuation in the number of trials conducted from year to year and due to special effects of the pandemic, we won't be able to say for at least two to three years whether or how many sponsors may be shifting their activities," emphasises Ruppert. For reasons of confidentiality, study sponsors and large CROs don't make any statements about CTIS even when asked. However, it is noteworthy that the world's largest CRO (IQVIA) said it will come out with a publication on CTIS very soon.

Europe can do better

Though it is possible to obtain EU marketing authorisation for a drug without study participants from Europe if the ethnic (Caucasian) background is provided, it is not known how EU HTA assessors would react to being confronted with exclusively ex-EU data during a benefit assessment. Sponsors will be bearing this in mind. According to pharma associations, it is important for Europe to strive to be a good location for studies simply because of access to and co-design of medical innovation, and to avoid dependency situations. Supply bottlenecks are a good illustration of what dependence on other countries can mean.

Krauss doesn't believe CTIS will change much, especially not in terms of user (un) friendliness. "There are many workarounds where you have to use other databases or systems – in short, it can be cumbersome and frustrating when applying," adds Ruppert. However, improvements to the CTIS system can only be made at EU level. Also, Ruppert points to other practical problems within the procedure: "It is actually the task of the reporting member state to consolidate queries and pass them back to the sponsor. We see that in some cases contradicting feedback from the participating countries is not resolved, but simply passed on by the reporting Member State. This may leave the sponsor a bit lost in some cases and wondering what to do. Some sponsors say that this – if this situation persists – might become a reason not to go to Europe," he adds. "The countries can ensure that the approval authority functions and that the ethics committee works smoothly. However, the implementation of changes is in the hands of the new EU Commission, which must create an appropriate framework. Additionally, we would like to see more projects like COMBINE from the new Commission, in order to improve the compatibility of trials that combine therapeutics with companion diagnostics and medical devices, and that implement real-world data." ■

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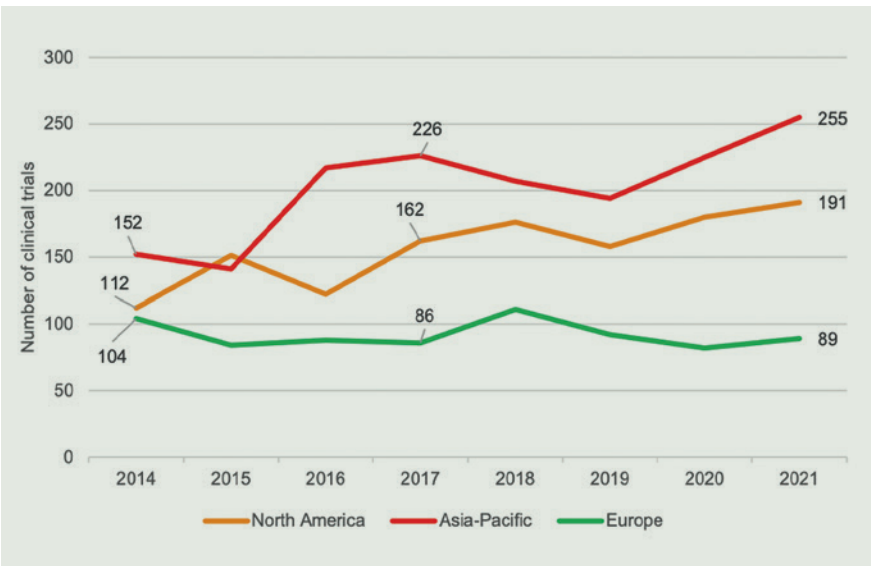


Figure 2: Geographic distribution of clinical trials involving cell, gene, and tissue engineering therapies (Advanced therapy medicinal products, ATMPs). China is leading the pack.

Picture: Alliance of Regenerative Medicine

SMEs suffer from CTIS

CTIS Born with the aim of harmonising the application, evaluation, and supervision process of clinical trials conducted in EU countries, there is much room for improvement for the Clinical Trial Information System CTIS, particularly with regard to SMEs and translational researchers.

› Ion Arocena, General Manager, Asebio

The Clinical Trial Information System (CTIS) was born with the aim of harmonising the application, evaluation, and supervision process of clinical trials in the EU, with an emphasis on their regulatory management. This is a European regulation with a long drafting process that begun in 2014, and was finally enacted in 2023, with the mission of enhancing Europe''s competitiveness in the field of clinical trials. Previously, each country had its own evaluation systems, which, from the promoters' point of view, resulted in a burden of repetitive dossier evaluations for every member state, a process made all the more complex by the differences in applicable protocols from country to country. This was cumbersome that this new evaluation process intends to harmonise.

The CTIS tool is very ambitious and has been very complex to develop. Currently, what we observe is that this tool is not functioning at full capacity. Yes, it is a functional tool that is meeting the needs of the European Commission in terms of a policy decision: to have a deadline for it to be fully operational. Therefore, priority has been given to ensuring that the tool is user friendly, rather than fully functional with all the features it could offer. It does the job today, but from the sponsors' point of view, there is much room for improvement before it becomes an efficient tool. Nonetheless, we believe that the European Medicines Agency (EMA) is responding to the needs identified during the deployment process.

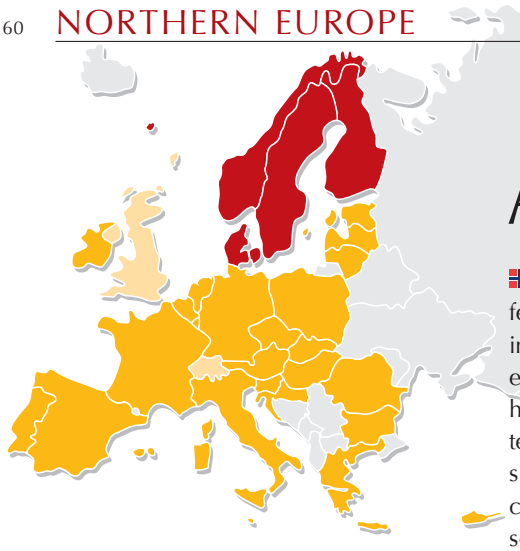
Despite this, concerns have been raised over the impact of this process on smaller companies, foundations focused on biomedical research, or independent researchers. The current system is acting to the detriment of research areas such as rare diseases or those with a lower prevalence among the population, which are not a priority for the big players but rather areas where SMEs and academic researchers play a key role. The entire European ecosystem of dynamic SMEs and academic researchers is suffering due to its lack of resources to comply with CTIS effectively.

Ion Arocena

Although the EMA has deployed a comprehensive training program, additional resources are needed to understand and comply with it. In this respect, we believe that a specific approach towards these smaller innovators is needed from the national medicines agencies to convey all this information. Therefore, these small entities are facing difficulties to gain access to external resources or initiatives to help them address the challenges of implementation. We believe that with regards to the responsiveness from national agencies, there is still room for improvement. The problem lies in the fact that there has been no financial allocation from Europe to the Member States to manage this sweeping transformation.

Regarding clinical trials that are in transition from EUDract to CTIS, the International Pharmaceutical Federation and a series of CROs have created a working group that is holding fluid discussions with the EC to streamline transition periods. We are aware that the EMA has addressed these requests and there have been some positive changes we positively value. However, we believe that there is still significant room for improvement so that it could also benefit smaller entities so that – with a more flexible framework – they would be able to transition their trials before the set deadline of January 31st 2025, a date Europe has unyieldingly refused to extend.

In this context, whilst deeply concerned that clinical research done in Europe might be in peril, we believe that we cannot allow ourselves to waver in our determination to avert this negative prospect. Europe is a high interest market for the pharmaceutical industry, and the incentives to improve the CTIS are high because it is in Europe's best interest, and the EU has the resources to do so. The EMA has been sensitive towards the needs expressed by the industry and some of the requirements have been recently amended. Now is the time to focus on the SME and academic research communities, providing national medicines agencies with the resources and the mandate to support smaller innovators in transitioning to the CTIS system. Europe's innovation largely relies in this group of smaller innovators, we just need to provide them specific training and support programs to help them comply and flourish under the new framework. ■



Fertile funding

WOMEN'S HEALTH Freya Biosciences, a biotech firm focused on women's health, has secured a US$38m Series A funding to further women's reproductive immunotherapies, marking one of the sector's largest raises. The investment, led by Sofinnova Partners and OMX Ventures, will propel the development of Freya's pioneering vaginal microbial immunotherapy for treating infertility in women with dysbiotic vaginal microbiota undergoing assisted reproductive technology. Additionally, the funding will enhance Freya's multi-omics data science platform for advanced microbiome sequencing and immune biomarker analysis in clinical samples. ■

Cancer pipeline

IMMUNOTHERAPY Clinical-stage biopharma company Nykode Therapeutics has added a vaccine programme for preventing and treating colorectal cancer to its pipeline. The potential first-in-class vaccine is based on the selection and combination of highly expressed tumour associated antigens involved in the development and progression of colonic polyps to colorectal cancer. Nykode's targeted immunotherapy platform is designed to induce broad CD8 T cell responses with the potential to overcome tolerance against tumour-associated antigens. ■

A cup of biotech

BIOPROCESSING Traditional coffee cultivation has a high environmental impact. It can lead to deforestation, soil erosion, and water pollution. Scientists have long explored biotechnological alternatives. Now, Finnish researchers have shown proof of concept for cell-based coffee production. The team at VTT Research Centre of Finland, led by Heiko Rischer have published the process of creating bioreactor-grown coffee in the Journal of Agriculture and Food Chemistry (DOI: 10.1021/acs.jafc.3c04503). The paper describes the process based on coffee plant cell cultures, and describes the roasting regimes as well as the flavour analysis and sensory profiling.

Apart from the favourable environmental footprint, the new process also has the potential to speed up coffee production significantly. Traditionally farmed coffee provides one or two harvests per year, while growing a batch from cells is possible within a month. It also yields more controlled harvests. However, the path to optimisation and EU approval of the more sustainable coffee is long: "It's one thing to grow coffee cells in a bioreactor," says Rischer. "Turning it into a commercially viable product is a completely different matter." He and his colleagues hope that the publication of their scientific article will spur the creation of an ecosystem that has the resources, expertise and motivation to develop a new way of producing coffee. ■

Missing results

ETHICS A new report jointly published by the AllTrials campaign, Cochrane Denmark, Norway and Sweden, the Dam Foundation, Melanomföreningen, and TranspariMED found that many clinical trials completed during 2016-19 in the Nordics either do not make their results public (22%) or delay the publication of such results. The report found that three quarters of all trials results were not made public within 12 months, ignoring WHO standards. Only 27% of all trials results were made public within 12 months of trial completion. "Not only is this lack of transparency in clinical trials a waste of increasingly scarce public funding, it harms patients and leaves gaps in medical evidence," stated the authors. "This makes it very difficult to determine how safe and effective treatments actually are." ■

Ally upgrade

DRUG DELIVERY DelSiTech Ltd., a clinical-stage drug delivery and development company, signed a global license and development agreement with Tolmar International Ltd. The US-based pharma company had just bought into DelSiTech in January, when they co-led a €10m financing round. Under the agreement, Tolmar will gain a global license to utilise DelSiTech's silica-based drug delivery technology platform for the development of two undisclosed long-acting injectable drug products. The company will also collaborate on controlled-release drug products based on Silica Matrix across various therapeutic areas, including urology, reproductive health, and pediatric endocrinology. DelSiTech will be eligible to receive upfront payment, development and commercial milestone payments, and royalties on net sales of licensed products. Financial details were, however, not disclosed. ■

Picture: valeria_aksakova on Freepik

Biotech merger mania

M&A Three new biotech mergers have mixed up the Nordic biotech scene.

Novonesis

A new Danish biotech company has emerged as Novozymes A/S and Chr. Hansen Holding A/S successfully concluded their merger, giving rise to Novonesis. The completed merger resulted in an upswing in share capital, now standing at DKK 936,597,292 through the introduction of new B-shares. Novonesis is gearing up for substantial financial growth, with aspirations for a 6-8% uptick in organic revenue by 2025 and an anticipated annual revenue of €3.7bn. The company aims to lead in innovating solutions for a healthier living, better food, reduced chemical use, and climate-neutral practices. "Novonesis combines our joint strengths and the wonders of biology, and we are set to lead a new era of biosolutions. We will innovate and develop transformative biosolutions that improve the way we all produce, consume and live," said Novozymes CEO Ester Baiget.

Calluna

Forbion spearheaded a €75m Series A financing for Calluna Pharma Inc, an Oslo-based biotech resulting from the merger of Dutch Oxitope Pharma and Norwegian Arxx Therapeutics. The newly formed company aims to develop therapies for inflammatory and fibrotic diseases. The merger united Oxitope and Arxx' expertise in innate immunity. Calluna focuses on disrupting upstream innate immune amplifiers, offering a safe approach to target disease-associated signaling pathways. The company's pipeline includes four selective antibodies, with CAL101 leading in Phase I trials for fibrosis and inflammation indications. The Series A was led by European VC investor Forbion, whose Operating Partner John Montana takes over as CEO. The company is also backed by Norwegian investors Sarsia, p53 and Investinor.

Calluna CEO John Montana

Picture: Calluna Pharma Inc.

3PBIOVIAN

In early 2024, Finnish Biovian Oy and Pamplona-based 3P Biopharmaceuticals Srl joined forces to build a pan-European Contract Development and Manufacturing Organisation (CDMO), dubbed 3PBIOVIAN. Backed by their common shareholder, Keensight Capital, the companies combine their expertise in the areas of viral vector production, microbial production of recombinant proteins, plasmid DNA (Biovian) and process development and GMP-compliant manufacturing of biologics and cell therapy products. The combined Group, named 3PBIOVIAN, will offer end-to-end development and manufacturing services for all protein expression systems and viral vectors from preclinical to clinical development and commercial production. Leveraging a joint 40-year track record, expertise, capabilities, and financial strength, the Group will position itself as a pan-European biologics CDMO, with gross sales above €75m. 3PBiovian SA activities will span across multiple platforms (microbial and mammalian expression, adenoviruses, adeno-associated viruses, cell therapy and plasmids) and offers enhanced production scale flexibility via a diverse range of bioreactor sizes. ■

NEWS

Mycoprotein factory

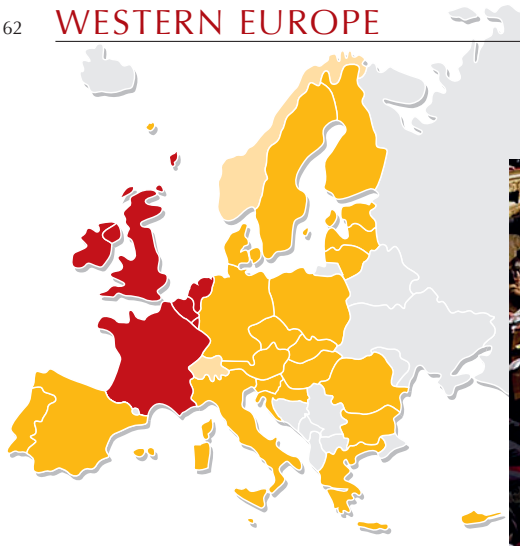
Microbial production specialist Enifer secures a €12m grant from Business Finland to construct a mycoprotein ingredient factory with an annual capacity of 300,000 tonnes. The NextGenerationEU funding will facilitate the construction of industrial facilities aligned with the EU's circular economy action plan, producing mycoprotein with significantly lower carbon emissions than traditional protein sources.

Catalent takeover

Novo Holdings, the investment arm responsible for managing assets and wealth on behalf of the Novo Nordisk Foundation, is set to acquire Catalent, Inc., a prominent player in the development and supply of medical treatments worldwide. Novo Holdings will purchase all outstanding shares of Catalent at $63.50 per share, adding up to US$16.5bn. The merger is expected to close towards the end of calendar year 2024

Rare disease venture

Swedish Orphan Biovitrum AB (Sobi) is set to establish a joint venture with South Korean pharma company Handok. Expected to be incorporated in the first half of this year, the joint venture will focus on the rare disease sector in South Korea and introduce Sobi's products like Empaveli, a targeted C3 therapy designed to regulate excessive activation of the complement cascade, and Doptelet, a thrombopoietin receptor agonist, to South Korea.



ATMP project

ATMP The Walloon Government has launched an €81m ATMP project over three years in collaboration with BioWin and the public service of Wallonia. The ATMP-PIT project brings together 26 partners for 12 work packages. Similar to the planned €44m German Strategy for Gene- and Cell Therapies (GCT), the Belgian project aims to improve networking and bundle the scattered R&D activities along the value chain. Around 60% of the budget comes from public funds, with 40% being privately funded. Almost €23m were allocated upon launch in December 2023. The ATMP-PIT encompasses cell, gene, exosome and phage therapies. The emphasis is on the suitability of planned developments for large-scale manufacture, with the effect of boosting Walloon businesses' own technologies, processes and products. The work packages address particular areas of scientific research with high development potential, preclinical and clinical research, as well as process design and control. Estimates predict that more than 470 direct jobs and 1,200 indirect jobs will be created over the next five years. The ATMP market expects to see a compound annual growth rate of more than 36% between 2019 and 2025. The market value is projected to reach €10bn by 2025 and €80bn by 2032. The Wallon region is home to 15 companies developing ATMPs, eight companies engaged in contract manufacturing and 15 service companies. Currently, the US, the UK and China lead gene therapy efforts. ■

Republicans fight biotech meat

CULTIVATED MEAT French parliamentarians from Les Républicains have lobbied in the National Assembly to ban all commercialisation of cell-based or cultivated meat in France (bill n°1965). The long-standing governing party is calling for "a ban on the production, processing and marketing of cell-based meat". Like the Italian government, the party cites the need to protect "agricultural production and food culture". According to the interest group Good Food Institute Europe, other countries such as Romania, Croatia and Austria are currently working on similar drafts. At the EU agri-minister Council in January, an alliance of 13 EU member states called on to tighten the rules for market authorisation of cultivated protein products under the Novel Food Regulation. However, GFI Europes spokesman Ivo Rzegotta said, the EU Commission seemed not amused about the move because the EU Novel Food Regulation is internationally recognised as one of the strictest food safety control systems worldwide. As it can take up to four years to Novel Food authorisation under this regulation to get market approval, EU food-biotech SMEs prefer to seek initial authorisation in Singapore, the USA or Israel where market approval is being granted regularly in under 12 month. In the EU Commission, there are even fears of a EU company exodus, which urgently needs to be addressed, according to Commission circles. The background to the initiative is likely to be the protection of the meat industry – France is the largest beef exporter in Europe. On the other hand, the coalition government, which lost its majority in parliament in the last elections, is apparently being persuaded to co-operate with Les Républicains, which have moved to the right. ■

Improving RNA analytics

CDMO Contract manufacturing of Moderna's mRNA COVID-19- vaccine was only the entrance gate for Lonza Group Ltd into the RNA drug space, as the company's former Chairman Albert Baehny underlined two years ago at Swiss Biotech Day. In the last week of-January, the CDMO took the next step hammering out a partnership with sequencing specialist Oxford Nanopore plc to speed up mRNA therapeutics analytical testing. Together, the partners will develop and market a rapid test to assess multiple critical quality attributes of mRNA products by directly sequencing both the DNA template and the messenger RNA (mRNA) itself. Nanopore-sequencing allows for the simultaneous measurement of several quality attributes in mRNA products on the same manufacturing site, potentially saving time to market. ■

Picture: © Richard Yang/Tanin Moriller - wikipedia.org

KRAS partnership

DRUG DEVELOPMENT Dublin-based Jazz Pharmaceuticals plc has ramped up its cancer drug portfolio with the acquisition of a KRAS inhibitor programme developed at British cancer fibrosis specialist Redx Pharma plc. KRAS mutatations occur in 85% of all tumour entities and worsen survial prognosis significantly. However, there are only few drugs because KRAS mutations are only indirectly accessible to drugs. Under the term of the agreement, Redx Pharma plc (Alderley Park, UK) will receive US$10m upfront and up to US$870m in milestone payments. Redx is also eligible for tiered, mid-single digit percentage royalties based on any future net sales. As part of a separate collaboration agreement, signed in parallel, Dublin-headquartered Jazz Pharmaceuticals plc will pay Redx to perform research and preclinical development activities. ■

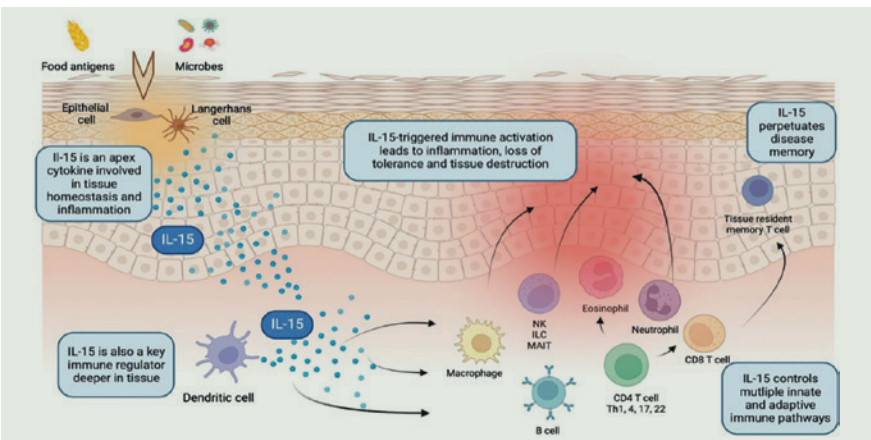
Fighting auto-immunity

IMMUNOLOGY Amsterdam-based Calypso Biotech BV has become the very next take-over candidate for Swiss Novartis AG. In January, the companies disclosed a plan under which the Swiss pharma giant is set to pay US$250m upfront plus of up to US$175m in milestone-dependent fees.

The acquisition would give Novartis AG full commercialisation rights to CALY-002, an antibody that blocks interleukin-15 (IL-15). IL15 controls an immune axis that controls barrier function and downstream immune cascades in many chronic autoimmune diseases such as viteligo, atopic dermatitis, but also primary sclerosing choliangitis, arthritis, or type I diabetes. Currently, CALY-002 is evaluated in a Phase Ib trial in patients with celiac disease and eosinophilic esophagitis. However, most competitors target IL15 in cancer immune therapies.

Calypso Biotch has been spun-out by Merck Serono in 2013 as specialist for inflammatory bowel diseases and other immunological indications, where the goal is to reduce inflammation and prevent tissue destruction.

Tissue-resident memory cells and other cells of the innate immune system that are controlled by IL-15 play an important role in the onset and maintenance of a large number of auto-immune, inflammatory and immune-metabolic diseases through control of Natural Killer cells and Memory T cells critically involved in disease onset and maintenance, as well as tissue destruction. ■



Picture: © Jabri & Abadie, Nat. Rev. Immunology (2015); Waldmann et al., J Exp. Medicine (2019)

Functions of IL-15 in tissue inflammation

NEWS

Synbio boost

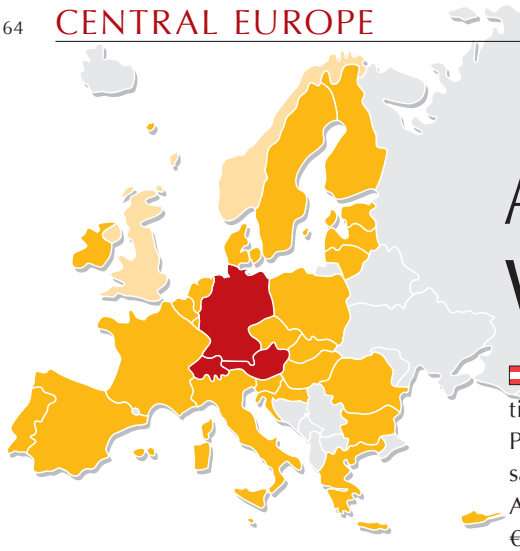
British Innovation Minister Andrew Griffith unveiled a £2bn strategic 10-year plan to foster engineering biology that lays out the government's strategy for turning the potential of cellular agriculture, New Genomic Techniques, medicinal advancements and sustainable fuel production into concrete benefits to the economy and people's quality of life. Redesigning biological systems has been identified as one of the five critical technologies being pursued by the government, as having the potential to grow at high speed.

Capital increase

In mid-February, hearing loss disorders specialist Sensorion SA has ramped up its cash reserves through the issuance of 88,594,737 new ordinary shares worth €50.5m to the benefit of Redmile Group, Invus and Sofinnova Partners, existing investors, Aquilo Capital, and two large investment management firms. The company will use the proceeds to advance its gene therapy program SENS-501 to Phase I/II testing, and GJB2-GT to start clinical testing in H1/2025.

Biodiesel revolution

British-Malaysian marine algae biofuel start-up HutanBio has secured an £2.25m seed investment to advance the production of its carbon negative biodiesel in first algae biofarms, possibly in Morocco or Australia. HBx biofuel oil is a low carbon fuel, which is made from auxotrophic marine algae. HBx biodiesel is a scalable high energy density, low carbon, sulphur-free, fuel solution, that uses CO_2 greenhouse gas as a feedstock.



TCR-injection

NASDAQ Immatics NV from Tübingen, Germany, announced a public offering for US$175m mid-January. Around 16 million ordinary shares were offered. The financing could rise to US$200m with several options for later purchase. The money is to flow into the clinical programmes with the company's own cell therapy platform. ■

Start-ups save Switzerland

START-UP Many start-ups in Switzerland faced a hard time finding investors last year. However, the biotech and medtech sectors were among the winners, according to the latest "Swiss Venture Capital Report" published by the online portal Startupticker. The report shows a particularly strong upturn in start-ups in the biotech and medtech sectors.

Investments in biotech start-ups rose by 22% to CHF492m in 2023 and in medtech start-ups by 41% to CHF379m. Of the 20 largest financing rounds last year, eight came from these two sectors, including the five biotech start-ups Noema Pharma, Alentis Therapeutics, Rejuveron Life Sciences, Nouscom and LimmaTech Biologics.

But, from a good CHF4bn in 2022, the overall financing in start-ups fell significantly for the first time to around CHF2.6bn – a drop of 35%. ■

Antiviral nasal spray from Vienna gets a boost

INFECTION Vienna-based G.ST Antivirals reports positive results from its Phase I clinical trial for the antiviral nasal spray with 2-deoxy-D-glucose (2-DG). At the same time, a Series A financing of €4m and a grant of €2m were raised.

The active ingredient combats rhinoviruses (RV), which trigger colds or more severe respiratory diseases in people who are particularly at risk, as well as other pathogens such as coronaviruses. This approach is based on reversing the manipulation of the host cell's metabolism triggered by the virus. Viruses do not have their own metabolism and are dependent on the host cell to reproduce. RV infections in particular switch on an anabolic state of the infected cells when they enter the host cell.

This upregulation of metabolic processes of the host cell, such as glycolysis, enables the virus to multiply rapidly. The inhibition of glycolysis by the glucose analogue 2-DG reverses the metabolic reprogramming of the host cells caused by the virus and prevents the virus from utilising the sugar, thereby significantly limiting its replication and consequently starving it. More clinical data shall be published until the end of the year. ■

Novartis invests €500m in Tyrol

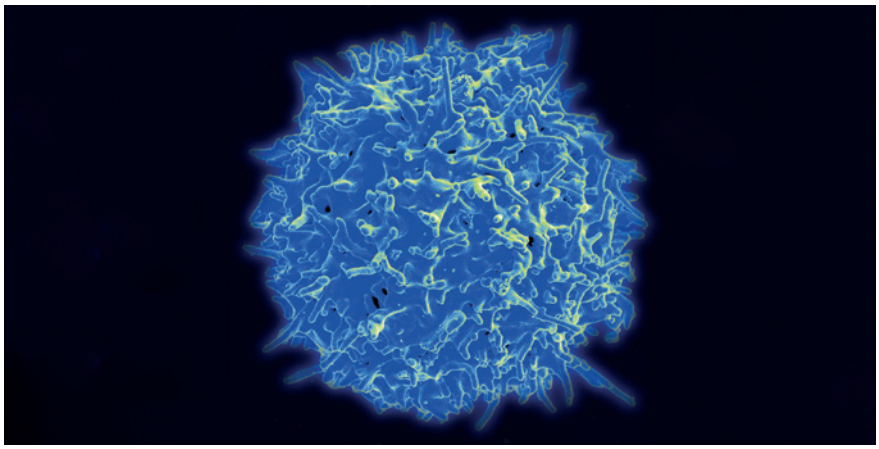
MANUFACTURING In order to "harmonise the production network with the strategy and the new technologies", Novartis announced planned investments of €500m with a focus on Austria. Two new cell culture facilities will be built at the long-standing Tyrolean sites in Kundl and Schaftenau. €250m will be invested in a facility in Kundl, which is scheduled for completion by 2025 and will create 180 highly qualified jobs. In Schaftenau (photo), the already planned investment totalling around 250m euros will be completed this summer, creating 165 additional jobs in production, quality and support functions. ■

Picture: © Novartis Austria

Combining T-cell expertise

IMMUNOTHERAPY German BioNTech acquired a stake to build a strategic cooperation with UK-based Autolus Therapeutics plc, which is listed on the US Nasdaq. The two companies are thus combining their developments in the field of CAR-T cell therapy, but also including other drug candidates. BioNTech is paying around US$50m upfront and plans to invest US$200m by acquireing shares of Autolus.

The collaboration also includes Autolus' manufacturing capabilities, which BioNTech may use on cost-effective terms to accelerate the development of BNT211 in pivotal studies in CLDN6+ tumours. In return, BioNTech will support the launch and expansion of the development programme of Autolus' advanced cell therapy candidate Obe-cel. The agreement gives Mainz options to co-commercialise Autolus' AUTO1/22 and AUTO6NG programmes as well as access to Autolus binding molecules and cell programming technologies including antibody-drug conjugates. ■



Healthy T-cell in the scanning electron micrograph

Picture: © NIAID/NIH

€60m for Swiss Timeline

REJUVENATION Amazentis SA/Timeline, a Lausanne-based biotech company specialising in longevity and healthy ageing, has raised €60m (US$66m) in an oversubscribed Series D financing round. The biotech company is developing solutions for healthy ageing and longevity under the product name Timeline. The investment was led by the L'Oréal Venture Fund (BOLD, Business Opportunities for L'Oréal Development) and Nestlé. BOLD is signalling great confidence in Timeline's proprietary Mitopure® technology, which is designed to ensure a longer and healthier life. .

Mitopure® is based on more than 15 years of research and, according to the company, has been clinically proven to slow down the ageing processes of cells and organs by specifically supporting the powerhouses of the cells, the mitochondria. Optimal mitochondrial function is one of the components of the molecular and cellular interplay of human metabolism known as a"hallmark of longevity" .

The organells are essential for maintaining cellular energy, resilience of immune system and other important benefits. "We have been an investor in Timeline since 2019 and continue to be very impressed by the team and the exponential potential of the Mitopure nutrition technology," comments Anna Mohl, CEO of Nestlé Health Science. ■

NEWS

CRISPR-Gentherapy

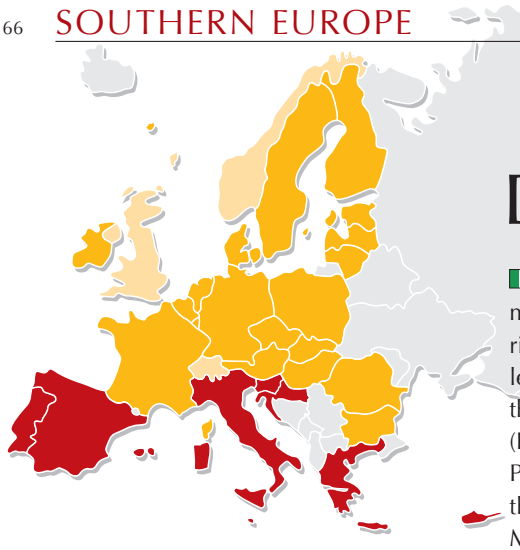
The EMA has approved the first gene therapy for the hereditary disease sickle cell anaemia. Austrian Biomay AG (Vienna) is involved in the production of Crispr therapy which is manufactured similar to the Lego building block principle. While some building blocks are manufactured elsewhere in Europe, the expertise of Biomay from Vienna is used for the Cas9 nuclease.

aCROss the channel

German FGK Clinical Research GmbH, a European full-service provider of clinical research services headquartered in Munich, has acquired Clinicology Ltd, a UK-based contract research organisation (CRO). This strategic move opens up new opportunities for both companies and strengthens their position in the European clinical research landscape, said CEO Martin Krauss. FGK and Clinicology have been working together for many years. The acquisition opens a path for FGK to set up clinical trials in the MHRA regulated area.

Infection

Swiss LimmaTech Biologics makes progress with Shigella vaccine and reports positive interim results from the Shigella4V (S4V) Phase I/II clinical trial with a tetravalent vaccine candidate. Shigellosis/diarrhoea particularly affects children in developing countries. S4V was tested in infants (9 months old) and showed a favourable safety and tolerability profile as well as sings of immunogenicity.



Biorefined

BIOFUELS At the end of January, energy specialist Eni SpA announced it will build Italy's third bio-refinery in Livorno. The project is awaiting official authorisations and includes the construction of three new facilities for the production of hydrogenated biofuels from organic waste: a biogenic feedstock pre-treatment unit; a 500,000 tonnes/year Ecofining™ plant, in which biogenic raw materials undergo hydrodeoxygenation and are subsequently isomerised, yielding HVO biofuel; and a facility to produce hydrogen from methane gas. The company did not announce if the hydrogen will be produced by steam reforming of natural gas or by methane pyrolysis, which consume high amounts of energy but emits zero carbon dioxide.

The conversion of the Livorno industrial site follows two conversions in Porto Marghera (2014) and Gela (2019) and aims at increasing the company's bio-refining capacity from currenly 1.65 million tonnes/year to over 5 million tonnes/year by 2030. Completion and commissioning of the of the three new bio-refining plants are expected by 2026. The plants will process biogenic feedstocks, mainly vegetable waste and residue, to produce hydrogenated diesel (HVO), HVO naphtha, which decrease CO_2 emissions by 90% compared to fossil diesel and naphta, and bio-LPG. Bio-LPG is produced from renewable sources. Eni's subsidiary Enilive is the second-largest producer of HVO in Europe and the third-largest in the world. The market is to expand by 40% by 2028. ■

Degradable fungal plastics

BIOMANUFACTURING Italian mycelium specialist Mogu Srl closed a Series A financing in January that was co-led by CDP Venture Capital (Rome) and the European Circular Bioeconomy Fund (ECBF VC), Kerixng Ventures (Paris), and Progress Tech Transfer also participated in the €11m financing. Upon the financing, Mogu will change its company name to SQIM Srl. The funds will be used to advance the company's platform (i.e. biological fermentation + biochemistry) and to accelerate industrial scaling, through the deployment and launch of a new demonstration-scale production plant. Additionally, the funds will be used to boost R&D efforts and staff.

Using mycelium, SQIM has developed a range of high-performance, low-environmental impact solutions, primarily addressing the textile, leather, interior, and automotive industries. More specifically, besides its brand MOGU, which is dedicated to interior design and architecture, SQIM produces EPHEA™, an entirely new class of animal-free alternatives primarily dedicated to Fashion and Automotive consisting of 100% mycelium biomass. ■

Picture: © Mogu

Gene therapy to fight obesity

OBESITY In January, Torino-based Resalis Therapeutics Srl has baged €10m in a Series A financing led by Sunstone Life Science Ventures (Copenhagen) to complete a Phase I study for RES-010 in obesity. Existing investors including Claris Ventures and angel investors participated in the financing The proceeds will be used to initiate and complete the first-in-human Phase I trial and reach Phase II readiness for Resalis' lead program, RES-010, in obesity.

RES-010 is a non-coding locked anti miRNA22 antisense-RNA designed to provide a disease-modifying approach in obesity with longer-lasting weight reduction and the ability to extend treatment durability in combination with approved therapeutics, such as GLP-1 receptor agonists and incretin boosters. Ablation of miRNA-22 protects against obesity-induced adipocyte senescence and ameliorates metabolic disorders in middle-aged mice. In tranferring white adipocytes into brown adipocytes, miRNA-22 deletion limits white adipose expansion and attenuates high-fat diet-induced fat mass accumulation providing a potentially more durable effect than incretin agonists. "Preserving muscle mass is key to provide a sustained and meaningful clinical benefit, and we share Resalis' vision that this non-GLP1/GIP therapeutic will significantly improve both effect and tolerability of today's therapies," said Claus Andersson, General Partner at Sunstone Life Science Ventures, who entered Resalis' Board. ■

Vegan meat on the upswing

FINANCING Barcelona-based food tech start-up Heüra Foods Srl has cashed in €40m in a Series B financing round supported by dutch Upfield Holdings BV, Unovis Asset Management (New-York), the food tech funds of the European Circular Bioeconomy Fund (Bonn, Germany), and Belgian New Tree Impact.

Heüra Foods develops plant-based meat alternatives that are aimed at sustainably changing the current food system and target the global protein transition. Heüra aims to lead growth in the alternative protein sector in Spain where it has achieved a 25% market share, it is consolidating its presence in key markets such as the UK, France and Italy. Its Mediterranian plant-based meat substitute portfolio has long been consisting of convenient food products made by high moisture extrusion from pea protein extracts, olive oil, a vegetable extract from beetroot, carrot, apple, as well as yeast extract, flavourings and methylcellulose, plus vitamin B_{12} and ascorbate as an antioxidant: example comprise the Rainbow Sandwich. Heura Bao, Heura nuggets, Heura curry, Pad Thai with Heura and Heura Burger.

Landmark technology

Based on its recently patented Good Rebel Tech, that prevents huge amounts of additives using "process-controlled microstructure design", the company has launched vegan ham style slices and Frankfurter sausages last year. "Our technology is a new way of texturising plant-based proteins and lipids without extrusion enabling us to create clean label products in categories that were impossible until now, in a scalable and cost-effective way," explains CEO Marc Coloma. "So for our ham, we don't need to use additives [such as hydrocolloids] to bind the product together. We can also use [the new technology] for cheese, pasta and a range of other products." In 2022, Heura's revenue rose by almost 80% to €31.4m, up from €17.7m one year before, as they ramped up distribution outside Spain. The latest cash injection is aimed at making the company profitable and strengthening its position in the plant-based food market, which is currently on the downturn due to high price, taste and texture problems compared to traditional meat and second generation cultivated protein products in the development pipeline. However, Coloma, who cofounded Heüra Foods in 2017 together with Bernat Añaños Fernendez, stated: "The investment shows us that our vision to be at the forefront of the protein transition in Europe is being recognised. To change the food system, we need to shift the pressure from consumers to the food industry and see health and sustainability as essential." According to Heüra Foods, its products enable "new nutritional values without additives" that can be applied to various vegan food categories, including sausages, meat and fish as well as dairy products. Remarkably, this ground-breaking method was first applied within just five months of submission of its patent application to develop the first additive-free 'York-style' product. This product has become the most rotated item per store/day in just three months.

No Novel Food

In General, times seem to get harder for producers of cell-based meat producers but not for Heura, whose products are not subject to the EU Novel Food Regulation as extracted pea protein is not regarded as a Novel Food. At the meeting of EU agriculture ministers in mid-January Austria, Italy and France called for stricter approval rules for cell-based Novel Foods and presented a non-peer-reviewed study questioning the positive climate footprint of fermenter-produced proteins. With the initiative, which is supported by 10 other EU member states that together collect around two thirds of the approximately €55bn in EU subsidies for traditional agriculture every year, the initiators want to ensure that traditional agriculture is given priority over the increasingly popular cultured meat alternatives. ■

NEWS

Fighting Alzheimer's

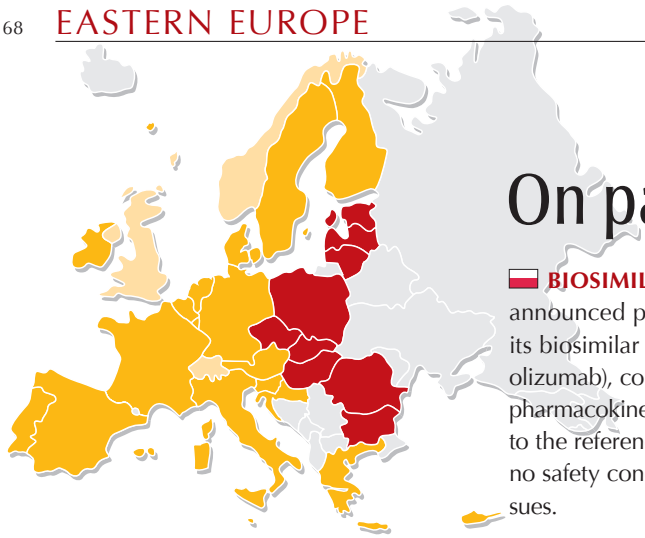
Patras-based ResQ Biotech has become the first Greek company to receive an ERC Proof of Concept Grant. The €150,000 will be used to advance the screening platform invented by team leader by the team Dr Georgios Skretas. It uses designer microbes to synthesise combinatorial libraries of cyclic peptides and screen them in order to find chemical rescuers of disease-associated protein misfolding and aggregation. The platform enables the screening of up to ten billion cyclic peptides that combine the advantages of antibodies and small molecules: high specificity, low toxicity and favourable pharmacokinetics.

CDMO heavyweight

In early February, Biovian Oy (Turku) and Pamplona-based 3P Biopharmaceuticals Srl have joined forces to build a pan-European CDMO named 3PBiovian. Backed by Keensight Capital, the companies will combine their expertises in the areas of viral vector production, microbial production of recombinant proteins, plasmid DNA (Biovian) and process development and GMP-compliant manufacturing of biologics and cell therapy products.

Taking over

Bologna-based Alfasigma SpA has closed the acquisition of the filgotinib business from Galapagos NV (Mechelen) that include 400 jobs in 14 European countries. Galapagos will receive €50m upfront, potential milestones totalling €120m and up to mid-double-digit royalities on EU sales. .



Patch collab

DIABETES Two Polish biopharma companies have made it their goal to transform the global diabetes market. Currently, insulin is being administered either orally or via injection. Biotts S.A. and BIOTON S.A. are now collaborating on an innovative transdermal delivery method. BIOTON is the world's top eight commercial manufacturers of recombinant human insulin, while Biotts brings its expertise in innovative carriers to the table. "The collaboration between our two companies from Poland demonstrates innovation which is ongoing within Polish Biotech and MedTec," commented BIOTON CEO Jeremy Launders. "Most importantly, transdermal technology gives wider choices on drug delivery systems to our patients." ■

Sharing data

RESEARCH The University of Tartu plans to establish a subsidiary called Estonian Multiomics Company (EMC) to foster innovation in healthcare. The EMC provides an avenue for people to contribute to groundbreaking healthcare services by securely sharing their health data. Trusted companies, vetted by the university, will analyse this data to develop new services and products. The university will hold a stake in companies, potentially earning profits for research funding. Additionally, the data may be used in the work of researchers and for providing health services in Estonia. ■

On par with the original

BIOSIMILARS Polpharma Biologics announced promising results for PB016, its biosimilar candidate for Entyvio (vedolizumab), confirming its comparability in pharmacokinetics and pharmacodynamics to the reference drug. The study revealed no safety concerns or immunogenicity issues.

Polpharma Biologics holds production facilities in Gdansk and Warsaw-Duchnice.

Vedolizumab is a monoclonal antibody that targets the α4β7 integrin, a protein found on gut homing T helper lymphocytes, reducing gastrointestinal inflammation. It has been approved for ulcerative colitis and Crohn's disease treatment, which are the two most common forms of inflammatory bowel disease. With PB016, a cost-effective alternative could make this treatment more accessible for millions of patients. Currently, a global clinical trial is underway to further assess PB016's efficacy and safety in patients with ulcerative colitis. Polpharma Biologics has a robust pipeline of biosimilars in various stages of development, addressing critical diseases in neurology, immunology, and ophthalmology. PB016 is Polpharma Biologics' third biosimilar to enter late-stage development. ■

Synbio advance

BIOENGINEERING Synthetic biology company Biomatter Inc., based in Vilnius, Lithuania, is making strides in Human Milk Oligosaccharide (HMO) production for infant nutrition. As the result of a collaboration with Kirin (Kirin Holdings Company Ltd.), researchers were able to selectively and efficiently produce HMO by engineered enzymes, especially one of the most abundant HMO in human milk – lacto-N-fucopentaose I (LNFP I). They published their findings in Metabolic Engineering (10.1016/j.ymben.2023.12.009).

HMOs are crucial for infant health, offering a number of benefits such as supporting gut health, boosting immunity, and protecting against infections. However, microbial production of long-chain HMOs like LNFP I poses challenges due to the formation of unwanted byproducts. In their research, the scientists addressed this issue and came up with a process for the production of LNFP I without the byproduct. ■

At-risk patients

STRATIFICATION A study by researchers from the Institute of Experimental Medicine of the Czech Academy of Sciences sheds light on the interplay between Alzheimer's Disease and SARS-CoV-2 infection. The study, done in collaboration with Finnish colleagues, was published in the Journal of Neuroinflammation (10.1186/s12974-023-02979-4). The scientists found that both AD patients and healthy probands were equally susceptible to an infection with SARS-CoV-2. However, an analysis assessing gene activity in cells from both groups infected under laboratory conditions with SARS-CoV-2 virus showed increased oxidative stress, suppression of inflammation, attenuation of immune responses and changes in olfactory-related genes in cells derived from individuals with AD. These findings suggest that people with AD may face more severe consequences of SARS-CoV-2 infection due to less efficient processes that suppress viral infection. ■

Liquid biopsy progress

CANCER DIAGNOSIS Blood tests for the early detection of cancer are on the upswing again after ways were found to recognise cancer-relevant patterns independently of mutations in individual blood cells with the help of artificial intelligence (AI). In December and February, major investments proved the confidence of investoras in new liquid biopsy technologies.

In February, multi-omics US liquid biospy specialist Freenome Inc. bagged US$254m in a financing round led by Swiss pharma giant Roche AG to fund early cancer detection in the "Vallania study" enrolling 6,200 patients. Frenome's hope is to detect patterns with its proprietary AI algorithm that seperates healthy volunteers from patients with early stage (I/II) cancer that is potentially curable. The size of the financing consortium shows that investors see great potential – both in terms of diagnosis and successful therapy – in the new AI-assisted blood tests: The US$254m funding round was joined by a16z Life Sciences Growth Fund, the American Cancer Society's BrightEdge Ventures, ARK Investments, ArrowMark Partners, Artis Ventures, Bain Capital Life Sciences, Cormorant Capital, DCVC, Eventide Asset Management LLC, Intermountain Ventures, Perceptive Advisors, Polaris Partners, Pura Vida Investments, Quest Diagnostics (NYSE: DGX), RA Capital Management, Sands Capital, Section 32, Squarepoint Capital, with funds and accounts advised by T. Rowe Price Associates, Inc., and others.

Harbinger Health Inc's co-founder Alex Meissner from Berlin-based Max Planck Institute for Molecular Genetics

Technical hurdels taken?

Despite technical hurdles in liquid biopsy-based early cancer detection tests, Swiss Roche AG sees potential in blood tests that are designed to detect cancer and tissue-specific biomarkers in cancer stages I and II where the disease does not mean certain death sooner or later. If it was possible to keep cancer in check through lifelong medication, this would be good news for both, business and patients. Distinguishing healthy from malignant stages by blood draws is ambitous as shown by Illumina's current US$7.1bn divestement from Craig Venter's start-up GRAIL (see European Biotechnology 04/23).

Freenome Inc, however, is leveraging a multi-omics platform, which uses computational biology, machine learning and other technologies to develop screening tools to detect cancer in its earliest, most treatable stages (I + II). The platform is currently being evaluated by Freenome's biopharma and diagnostic company partners to almost non-invasively detect minimal residual disease (MRD) augmented with biological insights derived from the multiomics platform.

In the Vallania Study, Freenome will enrol 6,200 participants including risk-matched control participants to reflect intended use populations. The study will compare blood samples to understand patterns associated with lung and other important cancers. Together with the diagnostics company Quest, Freenome have two registrational clinical studies running: PREEMPT CRC, that is enrolling more than 40,000-participants to prospectively predict the risk for colorectal cancer (CRC), and PROACT LUNG, a prospective observational clinical study recruiting up to 20,000 participants. The study is intended to validate Freenome's lung screening test in current and former smokers 50 years and older who are eligible for screening with an LDCT scan.

Early adopter

However, as classical mutation-based liquid biopsy tests were only able to detect cancer biomarkers in late cancer stages (III/IV), new technologies that focus on DNA methylation patterns in de-

Pictures: David Ausserhofer

velopmental genes that regulate a cell's fate in early development stage get more attention from investors. Last December, Harbinger Health Inc raised US$140m following a US$50m series A financing to evaluate such a test: According to its co-founder Meissner, Harbinger Health's test focuses on tissue specific detection of such cancer-specific CpG methylation patterns with a self-learning algorithm. "In a study involving 10,000 test subjects, we are investigating the DNA areas that are the first to be affected by the regulatory change when a normal cell degenerates into a malignant tumour. This is fundamentally different from looking at the change in a single gene during tumorigenesis. We are therefore not looking at mutations, but at the earlier re-regulation through DNA methylation. The second unique selling point concerns the possibility of detecting such re-regulation in body fluids. If you look at mutations, you have to be lucky enough to find a corresponding DNA fragment in the blood volume taken during the ten seconds of blood sampling. As we are not looking at one DNA region, but on thousands, it doesn't matter which one is in the blood volume taken, because they are equivalent in terms of significance. This means that we have a 1,000-fold greater chance of detection compared to looking at mutations. It is much more sensitive than classical cancer liquid biopsy that suffers from the low count of detectable cancer mutations detectable in the blood," he explains.

Targeting the methylome

Harbinger Health's test is based on the observation that the CpG islands are not methylated in placenta and cancer-specific developmental genes of healthy individuals, but are highly methylated in the invasively growing tumours and the placenta.According to Meissner, who works at the Berlin-based MPI for molecular genetics, the study will close in H1/2024. Harbinger Health aims to get a CLIA approval thereafter and in the mid-term go for FDA approval. ■

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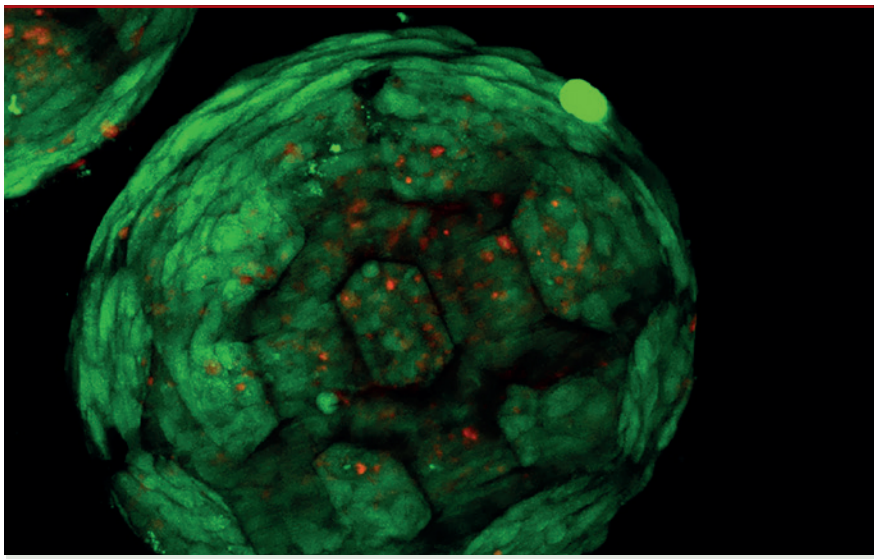


3D-printed cartilage

FIBROSIS Using a degradable soccer ball-shaped bioplastics matrix, tissue engineers at Techical University Wien have taken an important step towards the automated production of replacement tissue without functional limitations. In mid-February, they produced pressure-stable cartilage from stem cell spheroids embedded in the matrix, which had already begun the differentiation process into cartilage cells using a special 3D laser process. Normally, the fusion tendency of such cartilage cell precursors is limited, particularly due to the formation of a voluminous extracellular matrix. Because the cage-like structures for colonisation with pre-differentiated stem cells were tiny, they arranged as desired and connected seamlessly. ■

Allergy memory decoded

ALLERGY Danish ALK-Abelló A/S in a pair of papers have identified a unique type of immune cell as the hidden source of memory antibodies that drive many different types of allergies in humans. The team resolved the question: How does IgE antibodies, which are produced by short-lived plasma cells produce long-lasting allergies?

In a first study published in early February, Miyo Ota and colleagues described the discovery of a population of immune cells that sustain IgE production in children with peanut allergies. They examined immune cells from 58 peanut-allergic and 13 non-allergic children, and found that the allergic children had high amounts of type-2 polarised memory B cells, which expressed highly mutated B cell receptors that recognised the peanut allergen Ara h 2 and could quickly switch to producing IgE, suggesting these cells may explain the long-lived nature of peanut allergies.

Similarly, Joshua Koenig and colleagues discovered that these type-2-polarised memory B cells which expressed IgG1/IgG4, CD23, and IL-4R alpha, sustained allergic memory, in patients with birch pollen, dust mite allergies versus non-allergic people. Cells generated IgEs against specific antigens in some of the patients receiving sublingual immunotherapy for their allergies, thus showing that these cells act as a major reservoir for the antibody. A resuling therapeutic avenue would be to use allergen immunotherapy and biologicals targeting the IL-4-alpha receptor or IgE. ■

Cell death prevention

ALS German FundaMental Pharma GmbH has provided preclinical efficacy of its small molecule TwinF interface inhibitor, FP802 in the treatment of mice models mimicking amyotrophic lateral sclerosis (ALS). FP802 treatment resulted in reduced neurological scores and mortality in the SOD^{1G93A} ALS mouse model. Most importantly, the validated ALS clinical biomarker neurofilament light chain (Nf-L) was reduced in line with the positive treatment effects. Aditionally, FP802 protected human ALS patient-derived brain organoids from glutamate neurotoxicity, a key driver of ALS pathogenesis. "The success of FP802 in protecting ALS patients' brain organoids derived from human ALS patients underscores the translatability of our preclinical findings, offering a glimpse into the potential impact of TwinF interface inhibitors on patients," said Hilmar Bading, co-founder of FundaMental Pharma.

Toxic signaling by extrasynaptic NMDA receptors (eNMDARs) is considered an important promoter of ALS disease progression. TwinF interface inhibitors constitute an entirely new class of drugs that safely ameliorate glutamate neurotoxicity, a common cause of neurodegeneration. Contrary to classical NMDA receptor pharmacology, FP802 allows selective elimination of eNMDAR-mediated toxicity via disruption of the NMDAR/TRPM4 death signaling complex while sparing the vital physiological functions of synaptic NMDA receptors (10.1016/j.xcrm.2024.101413). ■

Picture: © Universita of Edinburgh

Spatial liver gene expression

FIBROSIS In January, Boehringer Ingelheim initiated the world's most extensive observational study that assess the development of liver fibrosis over two years in 200 participants with fatty liver-induced cirrhosis. The £30m ADVANCE study led by Quentin Anstee (left) from the University of Edinburgh is designed to identifiy new drug targets and treatments for this indication. The researchers will use initially drawn liver biopsies to compare tissue/single cell gene expression with the human Liver Cell Atlas, and conduct MRI and blood tests over 24 months to investigate what disease-related changes evolve in the body as cirrhosis progresses. A new AI tools scPoli from Fabian Theis' group at Helmholtz Munich might ease data integration. ■

Unhealthy plant-based meat?

STUDY European consumers seem to be concerned about the long-term health risks of ultra-processed foods. Most of the approximately 9,700 consumers from 17 countries surveyed by Ipsos on behalf of the EIT Health Food Consumer Observatory also include plant protein-based foods. Is Europe facing an acceptance problem?

A brand-new pan-European study "Consumer perceptions unwrapped: ultra-processed foods" may guide food-tech companies developing the next-generation of cell-based foods to respond to consumer fears. The report gives some guidance to food authorities, manufacturers and retailers to support consumers to make informed decisions.

Results of the survey across 9.700 consumers from 16 European nations including the UK plus Israel reveal that consumers across Europe are concerned about the impact of ultra-processed foods on their health. Yet, a lack of awareness, understanding and means are preventing people from making informed, healthy choices.

According to the survey, 65% of respondents from Belgium, Czechia, Denmark, Finland, France, Germany, Greece, Republic of Ireland, Israel, Italy, the Netherlands, Poland, Portugal, Romania, Spain, Switzerland, Turkey, and the UK believe that ultra-processed foods are unhealthy, and that they will cause health issues later in life – 67% believe that ultra-processed foods contribute to obesity, diabetes and other lifestyle-related health issues. What's more, 67% of respondents state that they do not like it when their foods contain ingredients they do not recognise, and 40% do not trust that ultra-processed foods are regulated well enough by authorities to ensure these foods are safe and healthy in the long term.

What is ultra-processed food?

Ultra-processed foods include packaged snacks, soda, sugary cereals, energy drinks and chocolate bars, as well as foods such as ready-made sauces and dips, ready meals and salad dressings. However, consumers also perceive plant-based substitutes for animal products, such as vegan cheese, also as ultra-processed because many contain ingredients such as protein isolates, seed oils, emulsifiers, gums, additives. Mushroom mycelium producers such as Hamburg-based Infinite Roots (former Mushlabs GmbH) have already addressed this perception using only five ingredients to "open up a healthier way to feed the world's population".

The survey also demonstrates that consumers believe that ultra-processed foods are bad for the environment, linked to the perception of artificiality because of industrial production. As this is in contradiction to what cell-based foodtech companies have demonstrated in peer-reviewed journals, they should intensify consumer information (see p. 3).

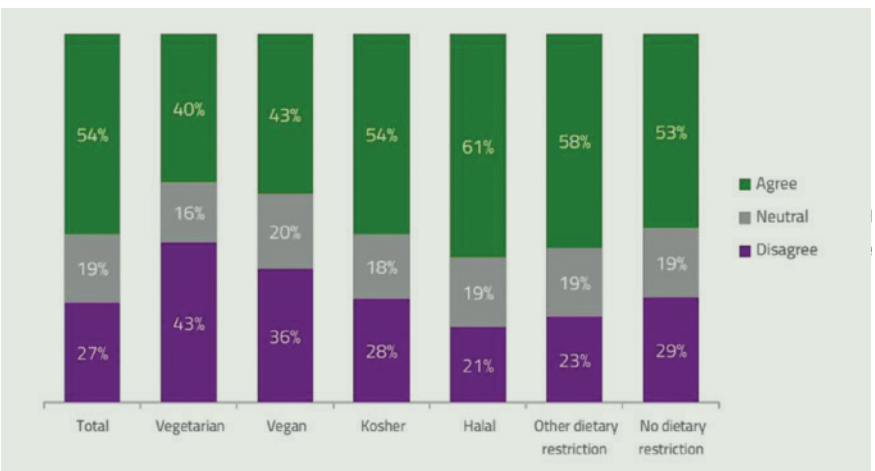
The consumer paradoxon

Despite serious health concerns, consumers continue to choose processed foods, with only 56% overall reporting that they try to avoid buying processed foods.

As well as convenience, price, and taste, the study shows that a lack of understanding as to how foods are processed is contributing to repondents' uncertainty when choosing which foods to buy. Furthermore, many are confused and uncertain about the extent to which their food is processed, both over- and underestimating how processed various food products are.

The survey also indicates that concerns over processing level are putting many consumers off choosing plant-based alternatives to meat and dairy products.

Vegetarian chicken pieces and vegan cheese slices are perceived as ultra-processed foods by 36% and 34% of respondents to the survey. Additionally, these foods were more likely to be seen as ultra-processed than their animal-based originals. More than half (54%) of the repondents to the representative survey do not eat plant-based substitutes because they want to avoid ultra-processed foods,



Response to the statement "I avoid plant-based meat replacements because they are ultra-processed".

Picture: © David Ausserhofer

particularly amongst meat and dairy eaters – but without any indication that they are choosing minimally processed plant-based options instead. Vegans and vegetarians, however, are less likely to avoid plant-based alternatives for this reason.

Finally, it seems that the willingness and ability to reduce ultra-processed food is limited. In a qualitative study, the Food Consumer Obervatory of EIT Health showed that the primary motivations for eating ultra-processed foods are their convenience, price, and taste. Many consumers prefer the taste of ultra-processed foods over home-made food, and see them as a treat.

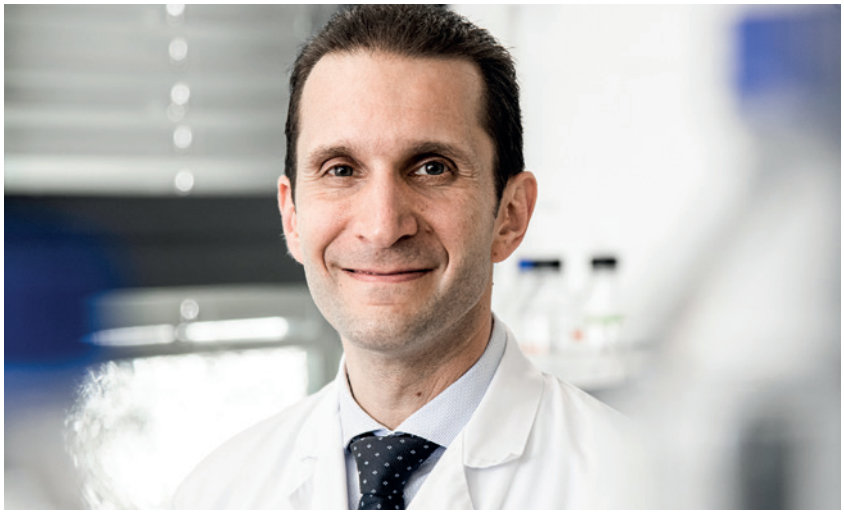
Recommendations

The study authors call on health institutions and scientists to define ultra-processed foods and make more conclusive and substantiated statements about their long-term health effects. Furthermore, they press for clarification whether plant-based substitutes are ultra-processed foods and whether this matters for their overall healthiness.

"It's […] crucial that we continue to bolster our understanding and agreement of how we classify, evaluate and label foods, so that our advice to consumers is informed by the latest science," commented Prof. Dr. Klaus Grunert (Aarhus University, the Director of the EIT Food Consumer Observatory.

Food-tech companies consider cleaner labels, with fewer 'artificial sounding' ingredients to reduce the association with being ultra-processed foods.

Manufacturers of plant-based substitutes need to consider that if consumers perceive a product as ultra-processed, this is hindering growth. Retailers can bring attention to packaged foods that are not ultra-processed. For example, within the plant-based substitute aisle, basically-processed foods such as tempeh, tofu, or falafel can be marked as non-ultra-processed foods.Retailers can additionally decide to not promote UPF ultra-processed products in their discount deals, and instead promote their minimally or even moderately processed equivalents. ■



Picture: © University of Zürich

Biomarkers for Long-COVID

LONG-COVID After US researchers uncovered last autumn that infections with SARS-CoV-2 may increase the risk of heart attacks and stroke by infecting artery wall tissue and macrophages that cause inflammations in atherosclerotic plaques, British and German researchers reported biomarkers that may diagnose Long-COVID.

At the end of February, British researchers demonstrated that Long-COVID is linked to persistently high levels of interferon gamma (IFN-γ). The study, published in Science Advances, followed a group of patients with Long-COVID fatigue for more than 2.5 years, to understand why some recovered and others did not.

New biomarkers

The team led by Dr Benjamin Krishna at University of Cambridge found out that initial infection with SARS-CoV-2 triggers production of the antiviral protein IFN-γ. For most people COVID-19 symptoms cease and production of this protein stops, but the researchers found that high levels of IFN-γ persisted in some Long-COVID patients for up to 31 months.

"We have found a potential mechanism underlying Long-COVID which could represent a biomarker – that is, a tell-tale signature of the condition. We hope that this could help to pave the way to develop therapies and give some patients a firm diagnosis," said Krishna.

According to Krishna, "IFN-γ can be used to treat viral infections such as hepatitis C but it causes symptoms including fatigue, fever, headache, aching muscles and depression. These symptoms are all too familiar to Long-COVID patients. For us, that was another smoking gun."

In January, a team headed by Onur Boyman (see photo above) from the University of Zurich reported new Long-COVID biomarkers identified in high-throughput proteomic analyses of the blood serum of 113 patients who had either fully recovered from COVID-19 or developed Long-COVID. Measuring serum levels of 6,596 human proteins in infected and healthy individuals immediately, six and twelve months after infection demonstrated an impaired activation of the complement system, altered coagulation and tissue damage, which in turn suggested persistent thromboinflammatory reactions in which monocyte-platelet aggregates showed elevated levels. Dysregulation of complement proteins could therefore contribute to the thromboinflammation associated with Long-COVID. To date, the use of coagulation and complement inhibitors has led to mixed results in the treatment of Long-COVID. Whether things will go better with the new targets remains to be seen. ■

CMO comes from Abbvie

ABIONYX PHARMA SA Dr Rob Scott, former Chief Medical Officer and Head of Development at AbbVie, joined Abionyx Pharma in January as new CMO and Head of Research and Development. Scott brings extensive experience in clinical development and regulatory affairs to the biotech company based in France and the US. Prior to joining Abionyx, Scott spent over thirty years in senior positions in the global pharmaceutical industry and biotech companies including J&J, Pfizer, Amgen. Most recently, Scott served as CMO at AbbVie and retired. There he also founded the Development Design Center, a centre of excellence focused on using predictive analytics and big data to design and conduct better clinical trials. Scott was a member of the FDA Advisory Committee on Cardiac and Renal Drugs and served on the Endocrine & Metabolic Committee from 2012 to 2016. ■

Rob Scott

Head of new division

SCANDINOVA SYSTEMS Uppsala-based ScandiNova Systems AB has appointed Pernilla Enkler as Head of Sustainability, Quality and Communication. Enkler took up her position at the beginning of 2024. She heads a newly established department covering sustainability, quality and communication. As head of division, Enkler is also part of the Executive Group Management and brings her extensive leadership experience gained in various industries, including start-ups and large international companies. Prior to joining Scandinova Systems, Enkler was CSO at Eternali and Head of Communications and Sustainability at Bellman Group. Apart from that, there are noch changes: Ulrika Sundén will continue as Head of Quality, while Erik Sundström will retain his role as Head of Brand, Communication and Marketing. ■

Pernilla Enkler

Interim CEO took over

EXSCIENTIA Drug developer Exscientia plc (Oxford, UK) has announced changes to its management team. CSO Dr Dave Hallett was appointed Interim CEO and Interim Principal Executive Officer in mid-February with immediate effect. The previous CEO Andrew Hopkins was dismissed by the Board of Directors with immediate effect. He is accused of having maintained two personal relationships with employees that were deemed "inappropriate and inconsistent" with the company's values. The search for a successor has begun. ■

Change in Management

ONECHAIN IMMUNOTHERAPEUTICS Stefanos Theoharis, Ph.D, joins OneChain Immunotherapeutics (OCI) as new CEO in February. He follows Jorge Alemany, CEO since 2022, when the Spin-off from the Josep Carreras Leukemia Research Institute has started in Barcelona. Alemany will now retire. OCI is specialised on the development of CAR T therapies for the treatment of oncologic diseases. Theoharis brings more than twenty years of experience in the field of cell and gene therapy, business development, program management and manufacturing. His career includes key roles such as Chief Business Officer at Bone Therapeutics, Senior Vice President at Cell Medica, and Chief Business Officer at Apceth Biopharma GmbH. He also held positions as Business Development Director at the antisense RNA drug company Isarna, and Business Development Director at Roche, focused on partnering activities for emerging technologies. Prior to this, he also worked at Lazard, the global investment bank, advising various life sciences companies on M&As and financing transactions. ■

Stefanos Theoharis

New CEO welcomed

STROMACARE SAS French biotech company StromaCare SAS has appointed Georges Rawadi as its new CEO at the beginning of February. Rawadi has more than 20 years of experience in the biotech and pharmaceutical industry, where he has held key positions. He was CEO and board member of the Belgian company Celyad Oncology. And he has also held various positions at Apmonia Therapeutics, eureKARE and Cellectis. Rawadi holds a PhD in Microbiology and an executive masters in Management and Strategy in the Healthcare Industry. ■

Georges Rawadi

Global union

LAUNCH The World Bioeconomy Association was officially launched during the World BioEconomy Forum in December 2023. Its mission is to serve as the central hub for stakeholders dedicated to advancing the multisectoral growth of the bioeconomy. The vision is to leverage the bioeconomy as a transformative engine, providing solutions to global challenges such as climate change, biodiversity loss, food security and health. ■

Freeing the way

LEGISLATION Assobiotec, the Italian biotech association, has joined the European Biosolutions Coalition, a strategic international alliance with the aim of identifying and overcoming the European regulatory obstacles that slow down the spread of biotechnological solutions in the agricultural and industrial fields. The coalition currently brings together industry associations with the goal to identify the legislative barriers for the development and marketing of bio-based products in Europe and the policy actions that are necessary to overcome them. ■

Investor school

TRAINING French health-care association France Biotech, together with the Health Innovation Agency, the General Directorate of the Treasury, and the "Tibi" Mission, has launched the "Investing in HealthTech" training programme, which covers aspects such as understanding the distinctive features of health-tech firms, navigating regulatory requirements, comprehending relevant business models and financing strategies, and recognising economic and health performance drivers. The overarching goal is to foster the emergence of robust financial entities in France capable of accelerating the growth of innovative health companies. ■

Inviting Collaboration: Join YEBN!

OPEN INVITATION Embracing collaboration as our cornerstone, the Young European Biotech Network (YEBN) proudly serves as an opportunity for life science enthusiasts across Europe to connect. For over two decades YEBN has been building bridges between academia and industry.

UPCOMING EVENTS

- **March 26, 2024, Gdansk/online**
  Session at S-DISCO days
- **April 6, 2024, Rome**
  Annual delegate assembly

YEBN thrives on the ethos of collabo_ration, recognizing that our collective strength lies in the diversity of perspectives and experiences within our community. As we continue to evolve, we recognize the pressing need for active participation from individuals and organizations alike. Your voice, your insights, and your contributions are integral to shaping the future of biotechnology in Europe.

A ripple effect of innovation

As we look to the future, our sights are set on expanding our reach and impact. We're committed to fostering collaborations with like-minded organizations to amplify our collective voice and influence. Through strategic partnerships and shared initiatives, we aim to create a ripple effect of innovation and progress that extends far beyond our borders.

As part of our commitment to enhancing collaboration and addressing the needs of the biotech community, YEBN is actively working to identify areas where we can make a meaningful impact. We understand that national and international biotech associations face a myriad of challenges, from navigating the complexities of fostering international collaborations to bridging the gap between the private and public sectors, and we are on a mission to meet the needs that biotech associations and help them join the international environment of Europe.

Learning what's missing

That's why we're dedicated to listening and learning from our peers in the different fields. We want to understand what's missing, what's needed, and how we can help. Whether it's through facilitating advertisement of employment opportunities or introducing new international collaborations, we're committed to finding innovative solutions that benefit the entire biotech ecosystem.

We invite you to join us in this journey of exploration and discovery. Whether you're a seasoned professional, a budding entrepreneur, a young scientist, or a curious student, there's a place for you in the YEBN family. Together, we can leverage our collective expertise and passion to tackle some of the most pressing issues facing the life sciences sector today.

To all who share our vision, whether as individuals, associations, or companies, we extend an open invitation to join our vibrant community. Let's chart a course towards collective growth and impact. Reach out to us at contact@yebn.eu to explore the endless possibilities for collaboration. Together, let's inspire, innovate, and influence change.

Save the date

And save the date! Our annual gathering awaits in the heart of Rome on April 6th—a day brimming with enriching discussions, engaging speakers, and pivotal advancements within YEBN, including the election of a new board. Don't miss this opportunity to connect, learn, and shape the future of biotech in Europe.

Visit our website at www.yebn.eu to learn more about the association. Your journey with YEBN begins now. ■

Join YEBN and make the difference!

Picture: © YEBN

An ocean of ideas

ASSOCIATION MEMBER Founded in 2006 as a start-up, Marinomed Biotech AG has successfully grown to a biotech company listed on the Vienna Stock Exchange. Marinomed's mission is to develop innovative treatments in the therapeutic areas of virology and immunology.

Marinomed develops innovative products in the therapeutic areas of virology and immunology.

Picture: © Marinomed Biotech AG

The former spin-off from the University of Veterinary Medicine Vienna has developed into a listed company with a headcount of around 50 employees and its own headquarters and laboratory space in Korneuburg, just outside of Vienna, Austria. Marinomed focuses on the validation of innovative therapeutic approaches, preclinical and clinical drug development, and subsequent out-licensing to partners. Based on its two proprietary and validated platforms, Carragelose® and Marinosolv®, Marinomed strives to develop powerful therapies for the treatment of indications with high medical need.

The solubilization technology Marinosolv® improves the solubility of hardly water-soluble small molecules and peptides, addressing one of the most challenging problems in formulation development. Marinomed has clinically validated the technology in the development of its own product candidates Tacrosolv (against ocular inflammation) and Budesolv (against allergic rhinitis). Besides that, Marinomed offers the Marinosolv® technology to external customers via its Solv4U technology partnerships.

However, Marinomed's success story started with Carragelose®, which was discovered by the founders in 2007 and has since been established as a globally marketed product portfolio with still a growing development pipeline.

The universal blocker

Carragelose® is iota-carrageenan, a natural polymer extracted from red seaweed which forms a protective and lubricating layer on mucosal surfaces such as nose, throat, or eyes. It is particularly well tolerated and strongly supported by extensive clinical and in-vitro studies. Data owned by the company have shown the virus-blocking effectiveness of Carragelose®, including major respiratory viruses such as Rhinoviruses or Corona viruses. Marinomed has developed a marketed portfolio of nasal and throat sprays as well as lozenges for the prophylaxis and treatment of viral respiratory infections. Next to its virus-blocking properties, the protecting layer formed by Carragelose® is also effective in shielding the mucosa from other external influences, such as pollen. Recent clinical data have demonstrated the benefits of Carragelose® in the treatment of allergic rhinitis. Furthermore, Marinomed has recently developed moisturizing eye drops based on Carragelose® for the treatment of dry eyes, further exploiting the potential of this versatile active ingredient.

KEY DATA
Marinomed Biotech AG (VSE: MARI)
Location: Korneuburg, Austria
CEO: Dr. Andreas Grassauer
R&D focus: Immunology & Virology
www.marinomed.com

From start-up to stock exchange

The success story from a small university start-up to a listed biotechnology company was only possible thanks to the great support of Austrian funding bodies and associations. In particular, the BIOTECH AUSTRIA association, which was founded in 2020, represents an important lobby for the Austrian biotechnology sector. BIOTECH AUSTRIA makes a significant contribution to advancing cutting-edge biotech research and supporting biotech companies in Austria. ■

BIOTECH AUSTRIA

UPCOMING EVENTS

- **April 9, 2024, Vienna**
  General Assembly (hybrid)
- **April 24, 2024, Vienna**
  3. BIOTECH CIRCLE AUSTRIA
- **May 15, 2024, Vienna**
  CEO Lunch

The power of collaboration

PLATFORMS The Swiss Biotech Association is committed to creating and maintaining platforms that benefit all Swiss biotech companies – not only its members – in branding, financing and partnering, search for talents, collaboration and networking.

As the Swiss biotech hub continues to grow, more than 100 biotech companies have joined the Swiss Biotech Association last year alone, expanding its member base by 25% to more than 500 members.

This is proof that the value of their platforms and member benefits is recognized and enables the association to effectively represent the interests of the industry. As strong advocate for the industry, emphasizing the significance of its innovation power and investment opportunities, the association is committed to creating and maintaining platforms that benefit all Swiss biotech companies, including non-members.

Promoting brands

In the public digital Swiss Biotech Directory over 1,400 Swiss Biotech companies are listed to increase their visibility globally by promoting their brand, products and services, and to open up new business opportunities. Additionally, the yearly print edition is distributed widely.

Financing and partnering

The Swiss Biotech Ventures platform connects Swiss-based R&D biotech companies with global investors and industry partners and facilitates financing and partnering. At the beginning of 2024, more than 800 investors and pharmaceutical companies were listed, and about 200 innovative venture projects from Swiss biotech companies were presented.

Talent search

Swiss Biotech Orbit helps to match job opportunities and talents, supporting all Swiss biotech companies offering job opportunities. Launched In 2022, the platform is constantly growing, opens doors to exciting opportunities for talents in life sciences R&D, and supports Swiss biotech companies in identifying them.

Onsite networking and international collaboration

The most powerful onsite networking platform, the Swiss Biotech Day, has developed into one of the leading global biotech collaboration conferences. In 2023 it attracted 1,800 participants. Close to 40% joining from abroad, representing more than 44 countries. The networking platform for international delegations – the Global Village – embedded in the Swiss Biotech Day, aims at facilitating international collaboration. With additional regular peer-to-peer meetings with biotech leaders and the Swiss Biotech Insight meetings, the Swiss Biotech Association brings people together to collaboratively shape the ideal framework conditions for a vibrant Swiss biotech community and beyond. ■

25 Years Swiss Biotech Association

SWISS BIOTECH

UPCOMING EVENTS

› **April 22-23, 2024, Basel**
Swiss Biotech Day &
Swiss Biotech Success Stories
Awards

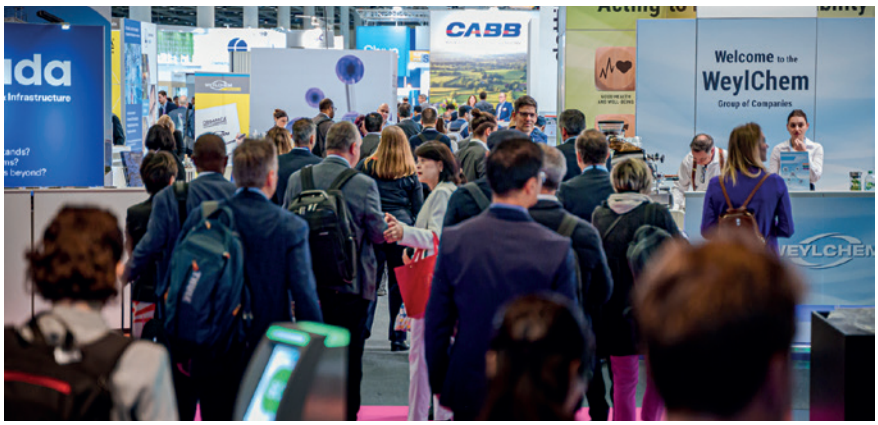
Pictures: © Swiss Biotech Association

Chemspec Europe 2024

NETWORKING Connect with the world of fine and speciality chemicals: taking place from 19-20 June 2024 at the Messe Düsseldorf exhibition centre in Germany, Chemspec Europe is the key marketplace to showcase the full array of fine and speciality chemicals, bespoke solutions, services, and equipment.

› Christiane Beck, Event Manager for Chemspec Europe, RX

Now in its 37th edition, the exhibition is an incredibly well-established fixture in the industry, drawing a highly specialised and international audience of purchasers and agents on the lookout for specific solutions, bespoke products and know-how exchanges with fellow industry colleagues. Chemspec Europe is an international event with a solid representation of Swiss, German, Austrian, French, Belgian, American and Indian firms. The exhibitor list includes Arxada AG, CABB AG, ESIM Chemicals GmbH, Midas Pharma, PI INDUSTRIES LTD, Robinson Brothers Limited, Saltigo GmbH (Lanxess), SEQENS SA, Society of Chemical Manufacturers & Affiliates (SOCMA), Weylchem International GmbH and many more.



Picture: 2024 Mack-Brooks Exhibitions - Part of RX, St Albans, UK

More than just an exhibition, Chemspec Europe provides a first-rate conference programme, enabling the exchange of expertise, interesting discussions on ongoing R&D projects and valuable networking opportunities. Organised in collaboration with renowned partner organisations, the conferences take place in six theatres, including:

- The Agrochemical Lecture Theatre
- The Pharma Lecture Theatre
- The Royal Society of Chemistry Symposium
- The Regulatory Services Lecture Theatre
- The Innovative Startups Presentations
- The EFCG Crop Protection & Fine Chemicals Forum

Further details on the conference programme will be released in due course. Chemspec Europe offers a Matchmaking Programme to enhance visitors' networking opportunities on-site. The matchmaking platform is an important time-saving tool for all those taking part in the show, aiming to connect visitors with exhibitors sharing complementary buyer and seller interests and allowing them to arrange meetings ahead of the event. Upgraded ticket options are available for an enhanced connection with other visitors via the Matchmaking Programme and will allow access to a Matchmaking Lounge, available on-site to Visitor PLUS ticket holders to join prearranged meetings.

Venue information

Chemspec Europe 2024 | Hall 3, Messe Düsseldorf, Germany

- 19th June 2024 | 09:00 - 17:00
- 20th June 2024 | 09:00 - 17:00

Before 5 June, the early bird ticket price of €50 is available, afterwards the ticket price increases to €85. On-site ticket purchases will incur a further rise to €100. The Visitor PLUS ticket, allowing for access to the Matchmaking Programme and the Matchmaking Lounge, is priced at €250.

Tickets are available here: www.chemspeceurope.com ■

WELCOME NOTE:
Christiane Beck -
Chemspec Europe Event Manager, RX

"The chemicals industry is one of Europe's largest manufacturing sectors and is actively involved in pioneering materials research, encompassing fields such as biochemistry and nanotechnology, with a strong focus on sustainability and green initiatives. Through the wealth of expert knowledge assembled both in the conference programme and among industry-leading exhibitors, Chemspec Europe 2024 is the ideal place to accrue the insider information necessary to remain competitive as the chemical industry undergoes significant transformations propelled by technological advances, digitalisation and environmental considerations."

Organoid research

MODELS Organoid technology has emerged as one of the most groundbreaking and cutting-edge technologies in the biomedical field. It finds widespread applications in disease modeling, drug discovery and screening, companion diagnostics, cell therapy, regenerative medicine, and more. Different cytokine combinations are introduced into the organoid media to obtain the desired organoids. These combinations modulate signaling pathways involved in organoid formation based on the cell source and the final differentiation type, for example, WENR (Wnt3a/EGF/Noggin/RSPO1) is the most classical cytokine scheme in organoid culture.

Sino Biological offers an extensive range of premium products, including over 800 cytokines, marker antibodies, ELISA kits, and antibody pairs. These products are tailored to support customers in the crucial steps of organoid culture, differentiation, analysis, and identification. ■

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order_eu@sinobiologicaleu.com
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34th ECCMID

27.–30.4.2024 BARCELONA/ONLINE European Congress of Clinical Microbiology and Infection Diseases (ECCMID) is one of the largest and the foremost congresses in the field of infection, bringing together more than 16,000 colleagues from all over the world for scientific education, networking and exchange. **www.eccmid.org**

27.3.24
Lab & Diagnostics of the Future, Stockholm (SE)
Info: Maria Eriksson, Life Science Sweden
http://labdiagnostics.eu/

10.-11.4.24
BOOM Summit, Basel (CH)
Info: DanOne/Kenes Group
https://boom-summit.com

9.-12.4.24
Analytica 2024, Munich (DE)
Info: Messe München GmbH
www.analytica.de

22.-23.4.24
Swiss Biotech Day 2024, Basel (CH)
Info: Swiss Biotech Association
https://swissbiotechday.ch

29.-30.4.24
BioVaria 2024, Munich (DE)
Info: Rebecca Engels, Ascenion GmbH
www.biovaria.org/

7.-8.5.24
Algen Summit 2024, Bern (CH)
Info: Swiss Food Research
www.swissfoodresearch.ch

12.-14.5.24
BioEquity Europe 2024, San Sebastian (ES)
Info: EBD Group/Biocentury
https://conferences.biocentury.com

22.-24.5.24
The MedTech Forum, Vienna (AT)
Info: MedTech Europe
www.themedtechforum.eu/

3.-6.6.24
BIO International Convention, San Diego (USA)
Info: BIO – Biotechnology Innovation Organization
www.bio.org/events/bio-international-convention

5.-6.6.24
Connect in Pharma, Genf (CH)
Info: Eleanor Gravette, Easy Fairs
www.connectinpharma.com/

12.-15.6.24
EuroScience Open Forum 2024, Katowice (PL)
Info: EuroScience/University of Silesia in Katowice/City of Katowice
https://www.esof.eu/

24.-27.6.24
EUBCE 2024 – 31st European Biomass Conference & Exhibition, Marseille (F)
Info: ETA Florence Renewable Energies
www.eubce.com

26.-27.6.24
World Bio Markets – Driving the commercialisation of the bioeconomy, Le Hague (NL)
Info: Paul McDonald, TNP Media Ltd.
www.worldbiomarkets.com

30.6.-3.7.24
European Congress on Biotechnology – Grand Challenges for Biotechnology: Health; Food Security; and Global Warming, Rotterdam (NL)
Info: European Federation of Biotechnology
www.ecb2024.com/

ACHEMA 2024

10.–14.6.2024 FRANKFURT AM MAIN With manufacturers and service providers from over 50 countries presenting their products for chemical, pharmaceutical and biotech research and manufacturing as well as energy and environmental services ACHEMA is the driving force for the international process industries and their suppliers. **www.achema.de**

10.-11.7.24
COURIOUS 2024, Mainz (DE)
Info: Future Insight e.V.
www.curiousfutureinsight.org/

11.9.24
The Future of Swedish & Danish Life Science, Lund (SE)
Info: Maria Eriksson, Life Science Sweden
www.swedishdanishlifescience.se

Chemspec Europe

19.–20.6.2024 DÜSSELDORF The international Exhibition showcases the entire spectrum of fine and speciality chemicals for various applications and industries. A first-rate conference programme accompanies the event and offers networking opportunities. **www.chemspeceurope.com**

25.-26.9.24
ILMAC 2024, Lausanne (CH)
Info: Sandy Mauch, MCH Group
www.ilmac.ch/de

8.-10.10.24
CPhI Milan 2024, Milan (IT)
Info: CPhI Global Office
https://www.cphi.com

10.-11.10.24
2nd BIOTECH SUMMIT AUSTRIA, Innsbruck (AT)
Info: BIOTECH AUSTRIA/ Human.technology Styria
www.biotech-summit-austria.com

11.-14.11.24
esib – European Summit of Industrial Biotechnology, Graz (AT)
Info: acib – austrian center of industrial biotechnology
www.esib.at

3.-4.12.24
BioFIT 2024/8th MedFIT, Lille (F)
Info: Margaux Satola, Eurosanté,
www.biofit-event.com/www.medfit-event.com

Pictures: Fira de Barcelona/ACHEMA/Messe Düsseldorf

Winners & losers

UK is investing £2bn in the new "National Vision for Engineering Biology" which sounds like a bold programme to bolster biomanufacturing, synthetic biology and process engineering.

EUROPE has not yet decided to follow one of the examples of strong governmental support of biotechnology. The UK themselves are following the US announcement of 2022 with Executive Order 14081 „Advance Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy", which is equipped with US$2bn to catapult industrial biotech production in the USA to the top of the world. Brussels, please wake up. ■

I'm in biotechnology because ...

CLAIRE MACHT,
Director, European Portfolio
EBD Group
"... human health is so complex, the only way to find treatments is through collaboration. Important players must work with partners who might be vastly different."

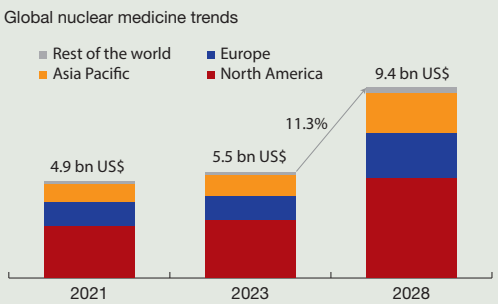
Long running

SWEDEN The Swedish Research Council gets go-ahead for more long-term funding. Following a government decision, the Swedish Research Council will soon be able to approve ten-year grant periods for funding research infrastructure, which may affect the giant Max IV project, among others. Until now, the Swedish Research Council's authority has been limited to granting research funding for a maximum of six years, but the authority's instructions are now being amended. This aims to improve the conditions for long-term planning of resources for certain essential infrastructures in the research area.

Long-term funding commitments are required, particularly concerning Max IV, the national laboratory for accelerator physics and research using synchrotron light in Lund, which is a facility that can be of particular benefit to life science research. ■

Nuclear medicine growing

According to a survey by MarketsandMarkets™ Inc., the global nuclear medicine market in terms of revenue was estimated to be worth US$5.5.bn in 2023 and is calculated to reach US$9.4bn by 2028, growing at a CAGR of 11,3% in the following five years. According to this study market growth is driven by the ageing population and increasing incidence of cancer and the need for early diagnosis of diseases for the elderly generation. ■



The really very last word

I don't know about the pessimists, but even I, as a notorious optimist, sometimes find it difficult to see the glass as half full. Biotechnologists are developing solutions to the global problems – just think of new foods from the bioreactor that could simultaneously alleviate the climate problem, secure global food supplies and save animals from mass captivity. Is that at the top of the agenda? Nope, it needs to be regulated for decades first. The same goes for NGT, i.e. CRISPR/Cas & Co., or modern biofuels. Clueless politicians and bureaucrats presume to decide which technologies should be realised. Why not define the goal and framework and then let the clever people work creatively? What about the KISS principle: Keep it smart and simple? And perhaps remember Montesquieu, who said: "If it is not necessary to enact a law, then it is necessary not to enact a law."

BERNADO GLAVO ■

Next issue 2024

SUMMER EDITION Innovations in drug discovery, bioprocessing and RNA medicines mirrored at ACHEMA together with the next must-attend events are the topics of our next issue. Players in these fields are invited to present their offerings in EUROPEAN BIOTECHNOLOGY MAGAZINE. Want to participate? Please contact Andreas Macht (+49-30-264921-54) or Oliver Schnell (-45) or drop us an email: *marketing@biocom.de*. Publishing date is 16 May 2024; deadline for ads is 3 May 2024. ■

Data source: Data from MarketsAndMarkets https://www.marketsandmarkets.com/Market-Reports/radiopharmaceuticals-market-417.html; Picture: © kora_ra_123 - stock.adobe.com (Icon); RockNRobin Photography

2ND BIOTECH SUMMIT AUSTRIA

CONFERENCE • EXHIBITION • NETWORKING

10-11 OCTOBER 2024

INNSBRUCK

CONFERENCE

Key Notes
Panel Discussions
Short Talks
Workshops

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