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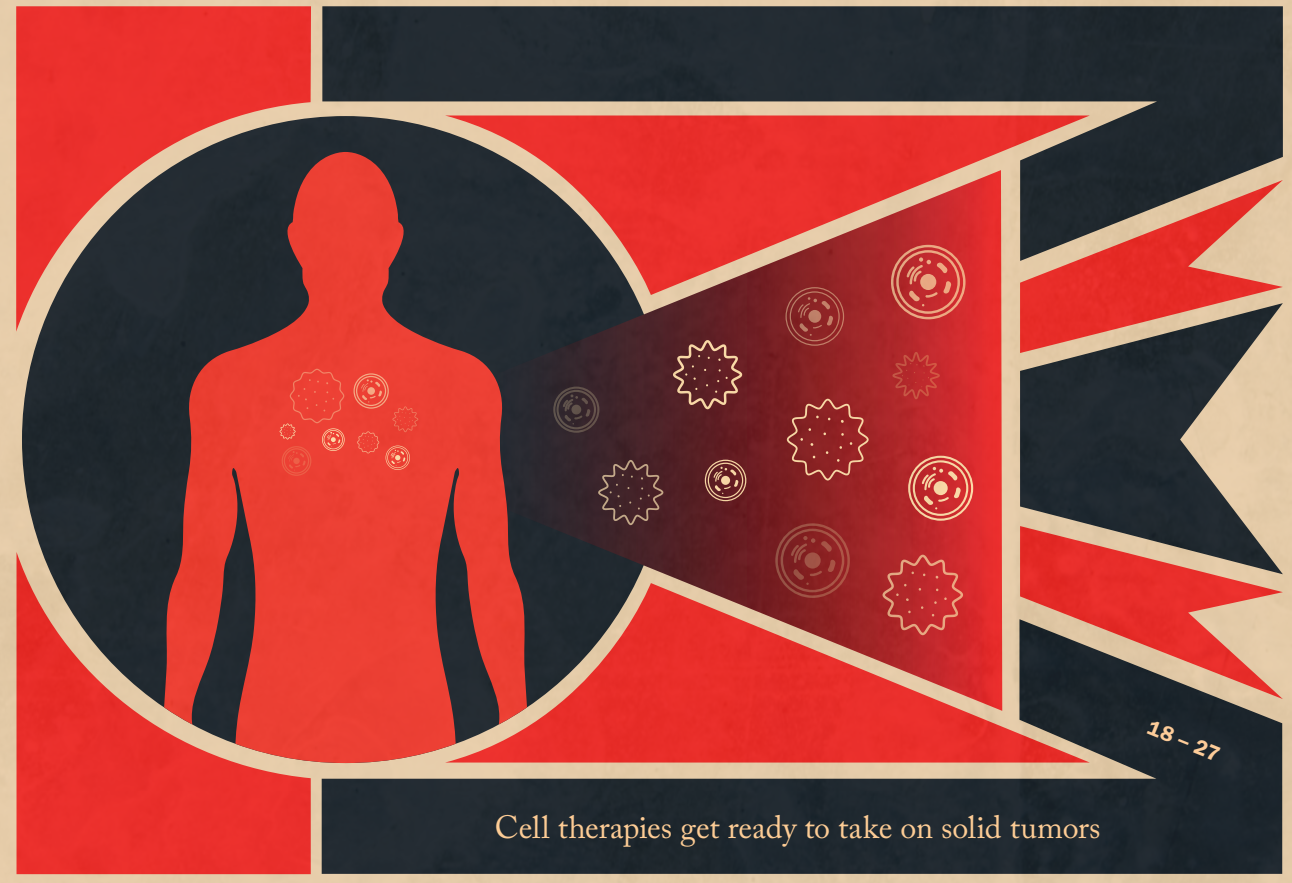

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A Hacker's Dream

Pharma sits on a wealth of highly valuable information. As the threat of digital infiltration grows, can the industry develop sufficiently effective strategies to ward off bad actors?

The drug producing sector thrives on innovation, and as companies build their pipelines and push products through the various stages of clinical development, patient data is amassed and new intellectual property is created. The industry's data is so rich that it has become the top target for cyber attacks, according to a new report (1). In 2020, companies in the pharma and healthcare sectors spent a whopping US$20.8 billion to address 92 ransomware attacks. We highlighted some of the shocking facts in an infographic in our July issue (2).

Clearly, cyber threat and digital theft is a relatively modern problem. But you may not know that the world's first group of hackers formed back in 1961. Though MIT's Tech Model Railroad Club (probably) did not have nefarious intentions when they adapted train sets to improve their function, some would argue they opened Pandora's box – introducing the idea that technology could be accessed and modified to fit a particular person or group's interests. The team went on to hack IBM operating systems, proving that the boundaries of digital exploration could be pushed (3). However, their work is a far cry from the actions of today's hackers. State-funded groups, as well as independent actors, pose an omnipresent threat to governments and businesses worldwide, including the pharma industry. Both AstraZeneca and Pfizer have reportedly been targeted by hackers, as have Indian vaccine makers – namely, the Serum Institute of India, and Bharat Biotech.

Cybersecurity has become an even hotter topic after Microsoft succumbed in August to Praying Mantis, a hacker who "exploits vulnerabilities in web applications" (4). This news came hot on the heels of recent attacks using an Israeli spyware tool, Pegasus. The cyber-surveillance product has caused much upset among international government, industry, and media circles.

Hackers do not remain stagnant in their approaches to infiltration. And as they continue to evolve, so too must the pharmaceutical industry if it aims to protect its digital assets. But companies will have to move quickly if they are to stand a chance of outpacing the digital predators that lie in wait. What does a truly rigorous line of defense look like? The answer isn't simple but increased awareness, training, and investment in the right resources are all steps in the right direction. We'll be exploring this in more detail in a future issue of The Medicine Maker. If you want to share your thoughts on pharma and cybersecurity, then please get in touch: maryam.mahdi@texerepublishing.com.

Maryam Mahdi
Associate Editor

References

1. *Deloitte, "Deal Breaker: Cyber Risk in Life Sciences M&A," (2021). Available at https://bit.ly/2VuZ9h6.*
2. *The Medicine Maker, "Security Threat," (2021). Available at https://bit.ly/3CezWbO.*
3. *Tripwire, "The Evolution of Hacking," (2016). Available at https://bit.ly/3A6ezHO.*
4. *CRN, "Microsoft Web Servers Targeted By Hacker 'Praying Mantis': Cybersecurity Firm," (2021). Available at https://bit.ly/2TUaU0n.*

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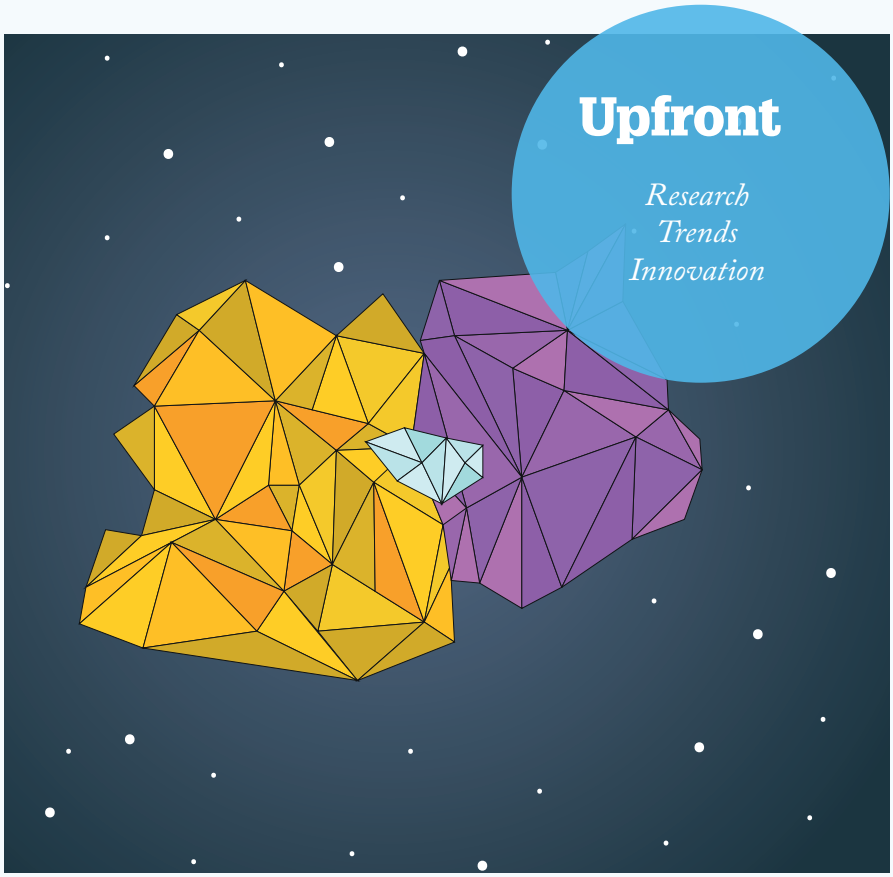


Marrying Up Proteins Using Molecular Glues

New research uses mass spec to identify new drugs that "glue" proteins together

Protein interactions underpin every function of the human body. When they go awry, disease results. At present, drugs that can sever these interactions – and therefore halt disease – do exist. But that's only half the story.

In some cases, absent or malformed protein interactions are the root of the problem and could benefit from drugs that serve as "glue" to bind relevant proteins together, restoring the correct balance of protein-protein interactions. Joint research undertaken by the UK's Universities of Leicester and Birmingham explores this concept further.

Aneika Leney, lecturer in biological mass spectrometry at the University of Birmingham says, "Richard Doveston, the other lead author on this work, is my husband, so [our departments] were a logical connection! The project largely stopped under lockdown because we were unable to enter the labs so could not perform any experiments, but we made the most of a difficult situation. It started with a conversation between my husband and I over a drink. We realized that a huge challenge in the 'molecular glues' field (his area of expertise) could be overcome using modern native mass spectrometry technology."

Using mass spec, Leney and colleagues separated out single proteins, protein-protein complexes, and any "glues" present. By monitoring what happened when adding a mixture of potential glues to the proteins, the team was able to identify which offered the best performance from within a single mass spectrum.

What's next? Leney believes that pharma companies can employ mass spectrometry as a screening tool to search for even more glues that can slow down disease progression or perhaps even treat disease.

Reference

1. *1. AC Leney et al., Chemical Science (2021). DOI: 10.1039/D1SC01450A.*

INFOGRAPHIC

Where Are the Generics?

Data from the Association for Accessible Medicines show that new generics are not readily available on Medicare Part D plans

The importance of generics

✖ Generic medicines saved the US healthcare system

$313

billion in 2019

✖ Generics typically cost

40-60%

less than branded counterparts

PHARMA CANNABIS IN BRIEF

What's new in the emerging field of pharma cannabis and cannabinoids?

- InMed Pharmaceuticals has signed a nonbinding letter of intent to acquire BayMedica, a private US company that specializes in the manufacture and commercialization of rare cannabinoids. The move follows developments from last year, in which InMed set up a collaboration agreement with BayMedica and the companies began sharing cannabinoid profiles and manufacturing processes.
- Singapore's iX Biopharma has announced its intent to spin off and list its pharmaceutical and medicinal cannabis business on the mainboard of the Hong Kong stock exchange. The spin-off will be called Ligo Pharma and will be engaged in the manufacturing, research, development, and sales of pharmaceutical and medicinal cannabis products. iX Biopharma will focus on sales, marketing, and distribution of nutraceutical products. Both businesses will be run by separate management and operations teams.
- MediPharm Labs has received a Drug Establishment Licence from Health Canada which, in conjunction with an already-awarded Cannabis Drug Licence, will allow the company to commercially distribute drugs containing cannabis in over 50 national markets, including the US and most of the EU.
- With "Project Change Lives," Clever Leaves has vowed to donate US$25 million worth of its product to researchers in the USA. The company has partnered with California's Biopharmaceutical Research Co., which has a license to import cannabis into the US. Clever Leaves also brought in a panel of clinicians to review submissions to a nationwide call for proposals from researchers seeking medical cannabis to conduct their studies.

Hope in the Fight Against Malaria

Trials of new malaria vaccine find high levels of durable protection

Are we getting closer to eradicating malaria? A team of US scientists led by Patrick E. Duffy at NIAID and Stephen L. Hoffman at Sanaria have conducted phase I trials of a malaria vaccine (PfSPZ) that offers a strong, durable protection for patients exposed to the disease (1). The vaccine is composed of sporozoites (the form of the malaria parasite transmitted by mosquito bites) and is combined with either pyrimethamine or chloroquine.

Of the two combinations, chloroquine appears to perform best. Among volunteers who received the highest PfSPZ dosage combined with pyrimethamine, 77.8 percent were protected from heterologous challenge, whereas 100 percent of those who received the higher PfSPZ dosage were protected.

A phase II trial is now underway in Mali, where malaria is endemic. At present no malaria vaccine is in widespread use, but the initial success of PfSPZ points to a promising future.

Reference

1. *A Mwakingwe-Omari et al., Nature (2021). DOI: 10.1038/s41586-021-03684-z*

Part D benefit dynamics may incentivize preference for brand products

	Annual List Price	Annual Net Price	Plan Liability
Brand	$22,100	$18,500 with -16 & rebate	$2,600
Generic	$13,300	$13,300	$9,600

Source AAM, "New Generics Are Less Available in Medicare Than Commercial Plans," (2021). Available at https://bit.ly/2VspnRs

Tier placement

✖ In 2021, over **60%** of 2020 first generic launches were placed in either non-preferred or speciality tiers in Medicare Part D plans, leading to higher cost sharing for patients

✖ In commercial plans, **98%** of 2020 first generics were placed in generic tiers

Nano-Origami Versus Infectious Agents

A team of researchers in Munich have found a way to trap viruses inside man-made nanomaterials

It was by serendipity that Hendrik Dietz, Professor of Biomolecular Nanotechnology at the Physics Department of the Technical University of Munich, and his team of scientists learned how to make a virus trap (1).

"We were working on building virus-sized icosahedral shells for several years (1, 2), and also on ways to produce many such objects (3)" says Dietz. "In summer 2019, I started thinking about applications and, well, it occurred to me: now that these things are virus-sized… how about putting viruses inside? And so we started testing this idea…"

The virus traps use nanocapsules to engulf and neutralize viruses, and have been tested successfully against hepatitis and adeno-associated viruses in cell cultures. Depending on the details of the trap design, they were able to reduce the activity of these viruses almost completely. Dietz hopes that the method could become a cheap, programmable, and mass-producible mechanical antiviral drug. Such a treatment may prove very valuable, since the vast majority of viral diseases have no cure whatsoever.

He also provided a helpful "recipe" for the traps:

- Make two virus-sized half-shells. These are made by programmable self-assembly with DNA origami.
- Coat the interior of the half-shells with molecules that have an affinity for virus surface features, such as antibodies, peptides, or host receptor domains.
- Add to virus! The virus will be sequestered by the shells like flies on flypaper. The virus is now encased and can no longer interact with cells.

Although the work began pre-pandemic, it's possible that the virus traps could also work against coronaviruses. Dietz and his team hope that their approach will reduce viral load in acute infections, offering a therapeutic benefit. The next step is to test the work in mice. Also on Dietz's agenda are the production of broad-spectrum shells with coatings that will stick to many viruses and virucidal shells that feature enzymes capable of degrading a virus' surface and rendering it harmless.

References

1. *H Dietz et al., Nature Methods (2021). DOI: 10.1038/s41563-021-01020-4*
2. *H Dietz et al, Nature (2017). DOI 10.1038/nature24651*
3. *Praetorius et al, Nature (2017). DOI: 10.1038/nature24650*

High Fines for High Prices

UK company fined for massively hiking the price of a generic drug

Advanz Pharma has been fined over £100 million by the UK's Competition and Markets Authority (CMA) for charging "excessive and unfair" prices for tablets used to treat thyroid hormone deficiency. From 2007 to 2017, the price of liothyronine tablets in Britain rose by more than 6,000 percent. Once the prices became unsustainable for the UK's National Health Service (NHS), the medicine was added to a "drop list," leaving many patients unable to access the treatment.

The CMA says that Advanz was able to sustain its progressive price inflation "because liothyronine tablets were among a number of drugs that, although genericised, faced limited or no competition and therefore could sustain repeated price increases… The price increases were not driven by any meaningful innovation or investment, volumes remained broadly stable, and the cost of producing the tablets did not increase significantly."

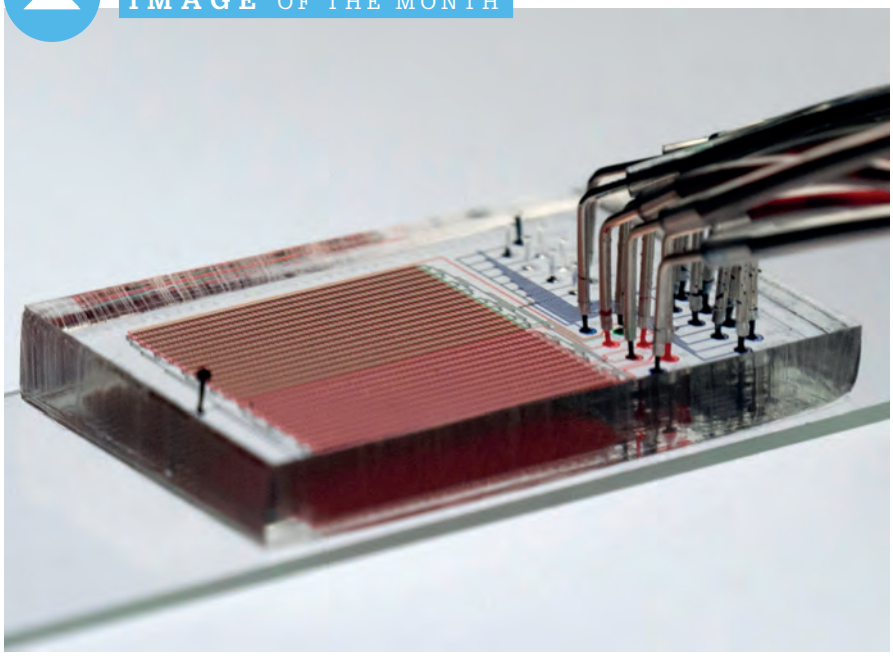
In 2006, the NHS spent around £600,000 per year on the drug. By 2016, it was spending more than £30 million.

Advanz says it will appeal the decision.

Reference

1. *Competition and Markets Authority (2021). Available at https://bit.ly/3rIXXTw.*

IMAGE OF THE MONTH



Enzyme Experiments

Researchers at Stanford University led by Polly Fordyce have created a new tool named the HT-MEK (High-Throughput Microfluidic Enzyme Kinetics) that can run thousands of enzyme experiments simultaneously. The technique combines two existing technologies: microfluidics, and cell-free protein synthesis.

Credit: Daniel Mokhtari

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Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"There's simply no justification for providing America's seniors worse access to lower-cost generics than beneficiaries in commercial health plans receive. The system prevents seniors from getting the full value of their Part D benefit. Policymakers should modernize Medicare Part D, remove policies that discourage use of lower-cost medicines and enact strong incentives for generic adoption."

The Association for Accessible Medicines in its July 2021 report discussing the availability of generic medicines in Medicare plans. https://bit.ly/2VspnRs

Keeping Pace with the Plague

Global regulators attend a virtual workshop on second-generation COVID-19 vaccines

Regulators worldwide are pushing for the development of new and improved "second-generation" vaccines against current and future strains of COVID-19. A recent virtual workshop held by the International Coalition of Medicines Regulatory Authorities (ICMRA) brought together leading global regulators to discuss what comes next. Participants discussed immunobridging, clinical trials, and immunity. They also touched on the authorization of second-generation vaccines and alternative approaches to demonstrate vaccine efficacy, expressing the need for alignment between regulators to respond to emerging COVID-19 variants.

The event was a follow-up to a workshop held in February 2021, which emphasized the role of data in speedily approving updated vaccines.

The participants reached a clear consensus: "Regulatory convergence is key to ensuring a consistent and timely response to emerging variants." A full summary of the workshop and its findings is available on the ICMRA website. Another workshop will take place later this year.

COVID-19 and Beyond: Focusing on a Patient-centric Culture

Sudarshan Jain, Secretary General of the Indian Pharmaceutical Alliance (IPA), discusses how the organization, along with its members, is working on adopting a more patient-centric approach to manufacturing

How have Indian drug developers responded to patient needs throughout the pandemic?

The pandemic has been a period of significant learning for the Indian industry. When a national lockdown was announced in early 2020, the government, pharmaceutical associations and industry leaders in India worked in an integrated manner to address the challenge of keeping the manufacturing operations and transportation working in order to maintain the uninterrupted supply of medicines. The industry also worked to ensure the safety of its employees and created safety protocols based on best practices.

Put simply, the industry responded promptly – evaluating whether available drugs could be repurposed and exploring more innovative approaches to working. Importantly, during the second wave of pandemic, when the demand for medicines surged, Indian pharma companies maintained the resilience and agility of supply chains so that patient needs could be catered to. The key focus, throughout has been to continuously upgrade systems and processes and supply quality medicines uninterruptedly by keeping patient-centricity at the heart of all operations.

However, although the focus continues to be on COVID-19, and rightly so, the industry is working towards ensuring the continued availability of all life-saving medicines.

In what ways is the IPA encouraging patient-focused manufacturing?

The Indian pharma industry strives to cater to the end-to-end needs of patients – keeping in mind value chain complexities and evolving consumer behaviors. Larger Indian pharma companies, for example, have been transforming their cultural practices to be more quality intensive. Workshops, periodic training and internal forum discussions have all helped improve awareness about patient-centric approaches among employees at all levels. The IPA has also taken steps to ensuring that patients have access to high quality, affordable medicines thereby contributing to advancing public health outcomes in India.

We established a Quality Forum in 2015 to assist Indian pharmaceutical companies in meeting international quality requirements. The team, which comprises representatives from some of the biggest pharma companies, meets to develop guidelines and share best practises on major quality, manufacturing and regulatory concerns. Several reports on manufacturing, quality, inspections, and regulatory filings have been produced by the Forum over the years in line with the industry's vision of becoming a global leader in quality as well as delivering the best patient outcomes.

"The Indian pharma industry strives to cater to the end-to-end needs of patients – keeping in mind value chain complexities and evolving consumer behaviors."

What will the future look like?

COVID-19 has reinforced that adopting a comprehensive patient-centric approach is the future and with digitalization pervading the industry at a pace far faster than ever imagined, this shift will be much more immediate than imagined. The pandemic has underlined the importance of collaboration among stakeholders and demonstrated how well companies are able to respond to unprecedented challenges. Learning from the second wave, the industry is preparing proactively and intends to be ahead in terms of drug availability by building reserve stocks and inventory of essential drugs.

Ultimately the COVID-19 pandemic has been an excellent opportunity for learning. Rather than firefighting, the industry can begin to address long-term concerns across the value chain before they become significant challenges. If we can increase competition, improve quality, and stimulate innovation in the market, we will ultimately be able to deliver better patient outcomes.

In My View

Experts from across the world share a single strongly held opinion or key idea.

Eliminating Bioconjugation Roadblocks

Bioconjugation of macromolecules to solid phase surfaces hasn't always been the most straightforward of processes. But to take vaccine and drug development to a new level, we need to find a better approach.

By Charlie Huang, Head of Diagnostics and Life Science at AnteoTech

Traditionally, vaccine and drug development has been a long, intensive process, partly due to difficulties associated with bioconjugation – the process that enables active macromolecules to be attached to solid-phase carriers or surfaces. Nearly all problems with bioconjugation can be traced back to the fact that not all biomolecules are compatible with the passive and covalent methods used in conventional approaches. Each type of biomolecule comes with its own set of challenges; the activity of some proteins, for example, can be impacted by passive and covalent conjugation, which can lead to irreversible chemical or structural modifications. These modifications can result in suboptimal conformation and presentation of target binding sites that limit assay performance and consistency. And when these processes are scaled up to manufacture multiple batches, inconsistent results are only amplified, creating reproducibility headaches for vaccine and drug developers. The fragile, complex, and inherently small nature of antigens can also be problematic, and some polysaccharides may not even have a functional group available for conjugation.

The fact of the matter is that currently used bioconjugation techniques are inherently slow. And in the midst of the current global health crisis, we can't afford to be held back. We need to eliminate roadblocks that affect these processes to rapidly develop the vaccines and drugs that are so urgently needed.

In my view, we should not hesitate to explore novel or alternative technologies designed to overcome limitations associated with conventional techniques – specifically, surface technologies that enable stable conjugation by forming multiple chelation and coordination points with both the underlying surfaces and the biomolecule of interest. This has already been made possible using polymeric metal ions that bind to available electron-donating groups on synthetic surfaces and biomolecules. The use of these ions will be essential in the industry's continued progress.

Already this rapid, single-step approach is being recognized for its ability to sustain biomolecule activity, as well as offer improved reproducibility and increased analytical sensitivity. Activated particles can remain coated and stable for up to 12 months, providing a welcome, simplified way forward for drug, vaccine, and high-sensitivity diagnostics development.

Confidence in such bioconjugation tools can also be derived from the growing catalog of diagnostic and therapeutic R&D efforts that have been made possible by these novel binding technologies. Adiponectin immunosensor development, tumor cell isolation, and extracellular vesicle research are just a few examples of the research areas benefiting from this approach. The advancement has also accelerated the testing of carbohydrates in vaccine development, as attractive

"We should not hesitate to explore novel or alternative technologies designed to overcome limitations associated with conventional techniques."

immune adjuvants that activate T helper cells. Previously, pH and buffer optimization were required to improve the conjugation efficiency of polysaccharides binding to multiplex magnetic beads. But this compromised polysaccharide binding activity – a common problem experienced when working with many carbohydrates. However, when using the nanosized molecular glue approach, polysialic acid – a polysaccharide commonly used in the field of vaccine research – bound to activated beads with an intensity far superior to that enabled by passive binding, paving the way for more efficient development of vaccines that leverage this carbohydrate.

It would be hard to find a more pertinent example of successful conjugation using this approach than the nucleocapsid protein (N-protein) of the SARS-CoV-2 virus. Recombinant SARS-CoV-2 N-protein is a critical antigen for developers pursuing diagnostic immunoassays, alongside other viral proteins, such as Spike S1 and Spike RBD (receptor binding domain). A recent study used the technology to conjugate recombinant Spike RBD of selected SARS-CoV-2 variants. It sought to understand the impact of COVID-19 vaccination on the levels of neutralizing antibodies against these RBD variants, and demonstrated that the nanosized molecular glue approach to bioconjugation provides a rapid and effective tool for SARS-CoV-2 multiplex immunoassay development for vaccine study (1).

For a long time, developers of vaccines, immunoassays and antibody-based drugs have battled with problematic proteins and biomolecules that were incompatible with conventional bioconjugation methods. To usher in a new era of rapid vaccine and biopharmaceutical development, however, we need to harness technology that allows us to break down the hurdles associated with bioconjugation and resultant delays in vaccine and drug development. By employing rapid and reliable bioconjugation solutions, there is a better chance that vaccines and drugs can be developed with the urgency required to get efficacious products to patients sooner, and combat any future pandemics.

References

1. *M Becker et al., "Immune response to SARS-CoV-2 variants of concern in vaccinated individuals" (2021). Available at: https://bit.ly/3cZy7oH.*

The Value of a Pack

As trials change and adapt, so too must clinical packaging. Companies must consider their design early on.

By Adrian Collins, Production Manager at Almac Clinical Services

Operating a clinical trial in a tightly regulated industry requires comprehensive, big-picture thinking. Risks remain at all stages of the clinical supply chain and can tip the scales from a successful study to no study at all. As businesses continue to navigate the COVID-19 pandemic, sponsors face challenges that require strategic planning – particularly when it comes to clinical packaging for small molecule drugs.

"The continued strong growth of small molecule drug development is challenging the industry narrative."

With so much focus in recent years on the emergence of biologics, it would be

easy to believe that the demise of small molecule drug development is imminent – but the continued strong growth of small molecule drug development is challenging the industry narrative surrounding their long-term viability (1). The pipeline for new drug manufacture continues to be dominated by solid oral dose formulations, with almost half (46 percent) of drugs in the development pipeline administered orally (2). Small molecules have also had the highest number of FDA approvals for decades and have accounted for around 70 percent of New Molecular Entities (NME) approved for use by the agency over the last five years (3). There are also more small molecule phase I trials taking place than ever before, with over 7,500 launched or entering development in the past five years (4).

Growth in small molecule drug development is great news for patients – especially in disease areas where investment is currently concentrated. However, it does raise the stakes for clinical trial sponsors when it comes to achieving a return on R&D investment. Increased competition, coupled with mounting study complexity, targeted patient populations, and investor-driven need for speed makes optimizing the processes that underpin successful trials management mission-critical – with several key factors for companies to consider.

Packaging requirements and processes are typically unseen or overlooked and, as such, are not given the necessary attention during a program's planning phase. Unique packaging strategies are needed for every study because products, protocols, and patients will vastly differ. The fact that different dosing formats are needed to accommodate tablets, capsules, inhalers, IVs, and injectors shows that there is no one-size-fits-all solution to this challenge.

Primary packaging can play an active role in helping sponsors reduce overages, plan for variable recruitment scenarios, and create robust forecasting strategies that enable contingency planning and de-risking of clinical supplies. Optimized packaging processes and access to expert design and guidance will also minimize waste and mitigate any negative impact on future stages of a study drug's lifecycle, including secondary packaging and distribution.

"Growth in small molecule drug development is great news for patients – especially in disease areas where investment is currently concentrated."

Where secondary packaging is concerned, access to expert kit and patient pack design, enhanced label generation, fully automated labeling, and production processes that reduce cycle time and promote compliance are all important factors for companies to consider – but this needs to happen early in the planning process. For example, packaging kit design can influence material, quantity, and tooling requirements, but the choice of kit is often restricted due to the stability of the drug product and its dosage form. Companies must understand these limitations from the outset to ensure that they are distributed without any hiccups.

The value of engaging early in a study's planning phase will be lost if companies cannot access expert services and technology and support sponsors to develop cost-effective, patient-centric packaging operations that keep pace with the demands of modern small molecule trials. From small companies to big pharma, a robust clinical packaging strategy will help keep ambitious trial timelines on track, minimize waste and inefficiency, and ensure continuous resupply to patients. It will also allow sponsor personnel to focus their attention on core business activity, reduce operational costs, increase regulatory compliance, and optimize processes to support expedited trial completion and return on investment.

Clinical packaging must be viewed as part of the bigger picture. Small molecules aren't going anywhere, but they have changed. We must therefore ensure that our packaging options are adopting to meet the changing needs of patients and sponsors.

References

1. *Global Newswire, "Biologics Market To Reach USD 625.6 Million By 2026 | Reports And Data" (2020). Available at https://bit.ly/3m1BnTb.*
2. *GlobalData, "Drugs in preclinical, phase 0, phase I, phase II, phase III, pre-registration or IND/CTA filed as of 16 Apr 2020 (includes drugs exploring multiple routes of administration)" (2020). Available at https://bit.ly/2PDHsce.*
3. *The Medicine Maker, "Small Molecules, Sizable Market Opportunities" (2020). Available at https://bit.ly/3swCGw1.*
4. *"Europe Small Molecule Drug Delivery Market Forecast to 2027" (2020). Available at https://bit.ly/39nLoVz.*

Continuous Progress

There are still barriers to the uptake of continuous manufacturing – but clear regulatory guidance can help companies overcome them

By Doug Hausner, Senior Manager, Continuous Manufacturing Business Development, Oral Solid Dose Pharma Services, Thermo Fisher Scientific, Greenville, North Carolina, USA

Continuous manufacturing is on the rise in pharma. Recent advances have made it possible to formulate a final drug product from base ingredients much faster without halting production. Continuous has proven its benefits for the manufacture of small molecule drugs, but there is now increasing interest in applying the technology to large molecules, too. The prospect of increased regulatory clarity and harmonization is also driving more organizations to take a hard look at continuous manufacturing.

Although manufacturers generally acknowledge the potential of continuous, there are barriers to adoption. In the last few years, the greatest challenge companies have had to contend with is working the upfront costs into business cases. The integrated lines required for a continuous process have a significant capital cost due to the need to bring in experienced personnel to handle the new technologies. For example, process development now requires more automation, as well as the use of process analytical technology and changes to the pharmaceutical quality systems. In addition, the lengthy timelines for setting up and qualifying a new line make it challenging to link a single product to a business case.

One of the uncertainties that hampers the adoption of continuous manufacturing is regulatory considerations. Though major agencies like the FDA, EMA, and PDMA have put forth guidance elements and strongly advocated for the adoption of continuous approaches, uncertainty remains regarding global market requirements. Years ago, it was a question of acceptance that stemmed from an overall lack of familiarity in many markets. Today, there is less concern about whether a continuous process will be approved; instead, concerns have shifted to questions about timelines and clarity on what information is really needed. For instance, ICH Q13, which has been in the works for a few years now and should be published within the next year, is intended to provide greater clarity for CM processing of both small and large molecules. Due to COVID-19, the group was unable to meet in person, somewhat delaying progress.

Another key consideration is understanding what batches are and how they are defined for continuous. "Batchless" operations are not necessarily possible in the strictest sense, because there still needs to be a way to delineate quantities of material produced to allow for alignment with traditional regulatory and PQS approaches. Where defining a batch is concerned, the degree of flexibility can present a challenge. Current guidance states that there are multiple acceptable ways to define a batch, as long as the definition remains consistent. It is often recommended that drug developers conduct a risk analysis and keep the batch size on the higher end of what would have been done with a traditional batch process. The tradeoff for shorter batch sizes is additional testing and documentation. For longer batches, higher development costs are expected.

In the end, however, batch size is not a critical factor, because what really matters is run time. Because batches can be produced in succession, many batches can be run in a series without stopping the process. Currently, the intended maximum run time is part of a submission and going beyond requires a filed plan or a post-approval change.

"One of the uncertainties that hampers the adoption of continuous manufacturing is regulatory considerations."

Many companies have stated, "We know we will be using continuous manufacturing in the future; we just don't know when that will be." The ability to wait is a function of the fact that the same product is being produced by either a continuous or a batch process. If these companies were enabling a new product using continuous manufacturing, adoption would be much faster. Those on the sidelines are always looking for ways to stick their toes in the water.

Today, continuous processes have been approved for both solid doses and drug substances. The gap from the initial approvals observed in the last few years seems to have resulted from first adopters' initially focusing on a single product and then turning to their early-stage pipeline. There are currently many late-stage compounds using continuous processes and we should see another round of approvals in the somewhat near future. This is an exciting prospect because it will demonstrate how first adopters have reorganized to embrace the technology.

Sustainability in Bacterial Endotoxin Testing (BET) – A Holistic Approach to Conservation and Recombinant Technology

How a holistic approach to horseshoe crab sustainability – involving non-animal alternatives to LAL, transparency, careful monitoring, and IVF programs – will allow the industry to maintain stocks while protecting patients

By Veronika S. Wills

Bacterial endotoxins can cause harmful symptoms, including fever and septic shock, if they find their way into a patient's bloodstream in sufficient concentrations. As a result, Bacterial Endotoxin Testing (BET) has become a fundamental safety requirement in the biopharma industry. Manufacturers must show that their finished products do not contain endotoxins exceeding the allowed limits.

The industry standard reagent for BET is Limulus Amebocyte Lysate (LAL), which is extracted from the white blood cells of the Atlantic horseshoe crab (Limulus polyphemus). For the past four decades, LAL reagents have been the only type of reagent approved by the US Food and Drug Agency to test for bacterial endotoxins. In recent years, however, a new class of BET reagents have emerged: recombinant reagents.

Recombinant reagents are non-animal-based and produced using recombinant DNA technology – an attractive proposition for manufacturers looking to reduce their environmental footprint. Thanks to the fact that the recombinant reagents are non-animal-based, they may yield more reproducible and repeatable data. But do they perform as well as the industry standard LAL? That question is still being debated by the subject matter experts, though published studies show extremely promising data. As alternative reagents for testing of products per compendia, the recombinant reagent used has to be shown equivalent to LAL for each individual product tested. This presents some significant regulatory burdens currently associated with recombinant reagents.

First and foremost, the FDA does not license recombinant reagents and will not accept their use unless a compendial test has been performed showing that the reagent is equivalent to LAL. Crucially, this must be done by the individual end user in their own lab – a significant drain on resources. In addition, companies may struggle to understand exactly what the regulatory expectations are, especially given that local regulations and regulatory authorities in different jurisdictions have varying expectations of what they would like to see from the end user when validating an alternative reagent. The regulatory requirements for LAL reagents were harmonized over 20 years ago, but this isn't the case for recombinant reagents.

We are hopeful that these requirements will be harmonized in the coming years – and there are several groups working on this – but compendial testing remains a significant hurdle to the more widespread adoption of recombinant reagents as alternatives to traditional LAL reagents.

Making life as easy as possible

Given the substantial regulatory hurdles associated with implementing an LAL alternative, Associates of Cape Cod, Inc. (ACC) have set out to make things as easy as possible for the end user. ACC's PyroSmart NextGen™ recombinant Cascade Reagent (rCR) is the first and only reagent available on the market that mimics the LAL cascade – the reagent's mechanism of action – completely. This rCR is based on the genetic sequence of Limulus polyphemus and reacts with endotoxins in the same way as LAL. It launched in spring 2021 and is now commercially available globally.

The time to result with PyroSmart NextGen™ can be reproducibly achieved for the sensitivity of 0.005 EU/mL in 60 minutes (including preparation and test time), whereas traditional LAL reagents usually take 85 minutes or longer and rFC reagents (first generation recombinant reagents) take around 110 minutes – though this can be cut to 74 minutes by using a plate with predisposed CSEs. Unlike first generation rFC recombinant reagents, converting over to PyroSmart NextGen™ (rCR) does not require any

changes to the user's current platform used for photometric LAL-based assays. The end user can use the same instruments and data analysis software as they do for traditional LAL; the only difference is the reagent. This really simplifies the process of demonstrating comparability with LAL. A considerable number of companies have joined ACC's evaluation program, which allows them to try the PyroSmart NextGen™ reagent and find out how suitable it is for testing their products while simultaneously collecting the comparability data required by regulators.

There is a lot of interest in alternatives to horseshoe crab-derived LAL reagents – especially as the industry as a whole has become more environmentally conscious over the past decade or so. But a combination of resources and internal knowhow limitations associated with proving comparability is a major hurdle that many end users simply cannot overcome – despite good intentions.

We are hopeful for greater regulatory harmonization to ease the burden on the end user but, until then, the process of adopting and proving comparability must be as straightforward as possible, and we are available to help with that process. We believe that allowing manufacturers to maintain their existing instrumentation and software platform will give more companies the option of choosing a non-animal-based BET reagent.

Veronika S. Wills is Manager, Technical Services at Associates of Cape Cod

Half a Century of Sustainability

Brett Hoffmeister, LAL Production Manager at Associates of Cape Cod Inc., explains how ACC are doing their bit to ensure horseshoe crab stocks remain strong

How are horseshoe crab stocks currently faring?

There are four species of horseshoe crab on the planet. Three of them exist in and around Asia – primarily on the east coast of the continent. The Limulus polyphemus species exists in the US, down into the Gulf of Mexico and part of the Yucatán. Though we don't have good data on the Asian species (there are some concerns over their status, given that they are used in food), horseshoe crabs are monitored very carefully in the US by the Atlantic States Marine Fisheries Commission (ASMFC). Individual states also have their own regulations and data collection efforts.

In the US, horseshoe crabs are mainly used as bait for conchs – carnivorous snails valued as seafood. Around 1.5 million crabs are allowed to be legally harvested for conch, this is allowed because the stocks are pretty healthy overall.

How does ACC help preserve their status?

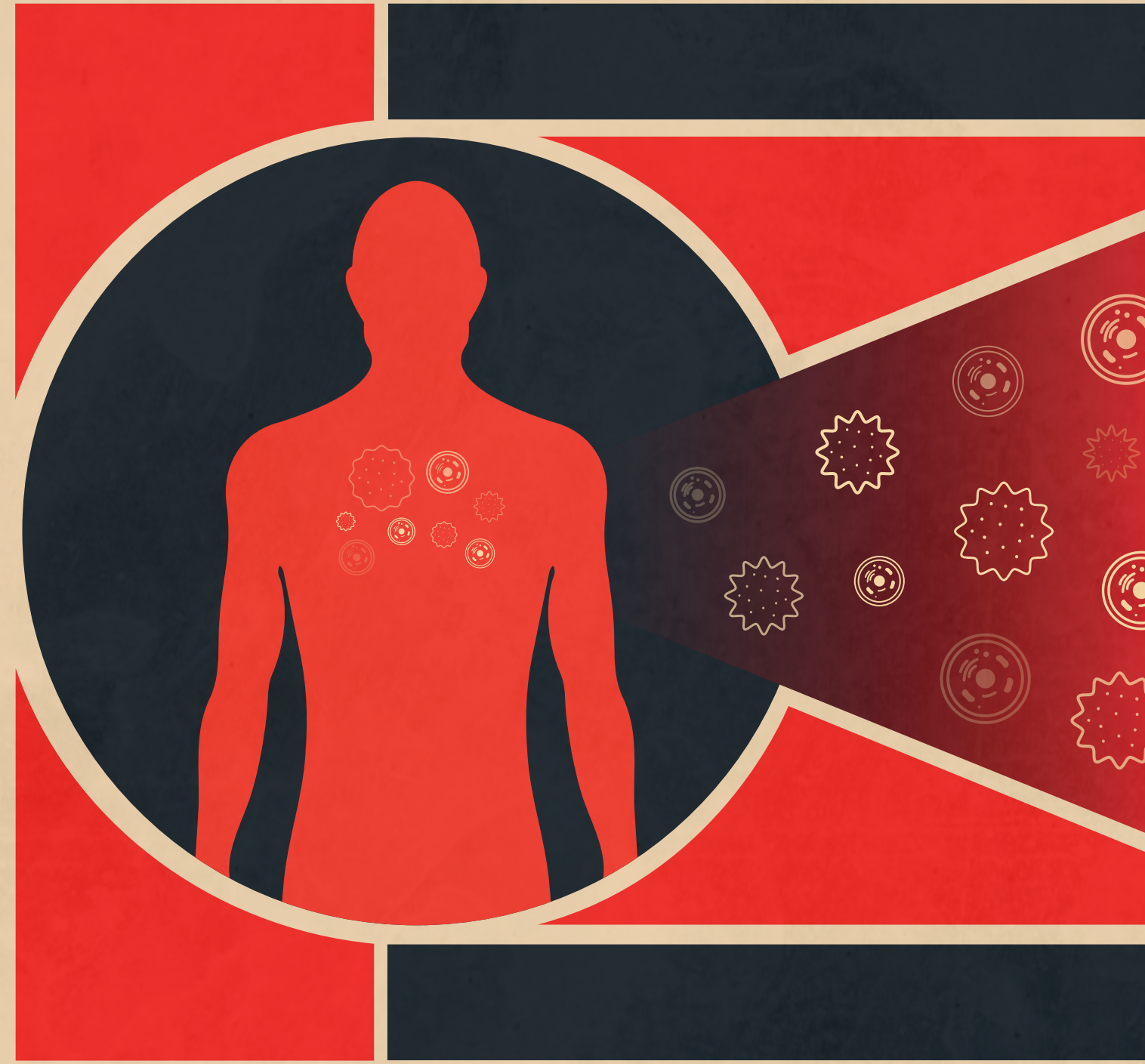
ACC was the first company to bring LAL to market over 45 years ago. Since the very beginning, we've had a catch and release policy in place. We work with fishermen to take the crabs from the wild, we treat them well, and we return them back to the wild. There's a lot of data that demonstrates that the crabs tolerate this process very well. For the past 20 years, we've been working closely with state and coastline regulators to implement conservation efforts to ensure the species thrives as the biomedical industry continues to grow.

Brett is currently Chair of the Atlantic States Marine Fisheries Commission Horseshoe Crab Advisory Panel; ACC has had members on the panel for the past 20 years. We share data on how many crabs come into our facility every day, the number of males and females, the vendor they came from, the body of water where they originated, and so on. Our facilities are also open to inspection and we take part in what's called a "market survey," which looks at crabs from different vendors to get a feel for the overall size of the crab stocks and identify how that trends over time. We have an open-door policy that helps regulators do what they need to manage the fishery.

Tell us about your unique horseshoe crab fertilization program…

We started this sustainability project three years ago; it's the only large-scale horseshoe crab in-vitro fertilization (IVF) program in the US. There are some crabs that come into our facility that originate from the bait market. We extract some of their blood, but we also extract some of their eggs, which we fertilize in vitro. We let them grow to the point where they have a good chance of survival in the wild and then release them. We are very excited to have reached a major milestone this year with the release of our millionth crab into the wild!

We're proud to continue the work ACC has done over almost half a century to preserve and protect the horseshoe crab.



COMPLETING *The* CELL THERAPY REVOLUTION

With no specific antigens available and a highly immunosuppressive microenvironment with little blood flow, how will researchers tackle solid tumors and bring cell therapy to millions?

By James Strachan

In 2017, the pharmaceutical industry erupted in celebration as the FDA approved the first two CAR T-cell therapies, Yescarta and Kymriah. Until then, the prospect of extracting a patient's cells, modifying them to express chimeric antigen receptors on the surface, and reinfusing them into the patient to latch onto specific antigens to kill tumors had seemed like science fiction to many. But FDA approvals answered the doubters: CAR T works.

However, other questions remained unanswered. Ideal drug manufacturing and logistic processes are closed and automated to eliminate the risks associated with human intervention and manual operations – but this is not the case with autologous CAR T. So how would companies handle living, breathing cells in transit? Would healthcare systems be able to cope? Pricing too was a concern. Would all stakeholders embrace evidence-based pricing?

Though these questions are yet to be fully resolved, we are seeing a conversational shift back to where it all began: scientific efficacy. We know cell therapy works in liquid tumors (leukemia and lymphoma), but what about solid tumors, which represent approximately 90 percent of adult human cancers and, therefore, a huge area of unmet need. In short, what's the hold up?

"We all thought solid tumors might be a little bit harder – but how hard could it really be?" asks Bruce Levine, Barbara and Edward Netter Professor in Cancer Gene Therapy at the University of Pennsylvania, and President of the International Society for Cell & Gene Therapy (ISCT). "Quite a lot harder, it turns out."

The central challenge is antigen specificity. The first CAR T-cell therapies were approved for beta cell-malignancies, which have easily identifiable surface markers, such as CD-19 or BCMA. An anti-CD-19 CAR T-cell therapy may wipe out most of a patient's B-cells in addition to their cancer, though this isn't a major problem. "But if you found a target that was unique to lung tissue, for example, you couldn't easily treat it with a T cell therapy because you'd run the risk of also seriously damaging the patient's lungs," says Elliot Norry, Chief Medical Officer at Adaptimmune.

Some targets, such as EGFRviii, are tumor specific – so attacking these does not risk wiping out the patient's organs. However, they're only present in about a third of glioblastomas. Finding a target that is both tumor specific and homogeneously expressed has vexed developers looking to target solid tumors. The first blood cancer cell therapies were far less challenging.

"You need to be looking at multiple targets," says Levine. "But you also need to titrate those targets." He raises the example of mesothelin, which is expressed in pancreatic adenocarcinomas, mesotheliomas, ovarian cancers, and about half of lung cancers – plus others. The catch is that mesothelin also exists at lower levels in the pleural cavity, which means any potential cell therapy targeting it could be destructive to a certain degree if not titered or controlled.

Another hurdle is the highly immunosuppressive solid tumor microenvironment, which includes the expression of checkpoint ligands, the secretion of immunosuppressive mediators like TGF-beta, the presence of regulatory T cells, and myeloid-derived suppressor cells – all of which conspire to prevent the immune system from detecting and killing the tumor. To make matters worse, solid tumors aren't well vascularized; the stroma is tightly packed and resistant to penetration by immune cells because of a matrix of cancer-associated fibroblasts.

But Levine thinks we have strategies to combat each of these problems. "It's going to take a combination of strategies and targets, including synthetic biology. The route of administration may be important too," he argues. "I'm optimistic because we do see evidence of clinical activity in both preclinical models and some early clinical trials."

"Solid tumors are the field's holy grail right now," says Tony Ting, Chief Scientific Officer at Bone Therapeutics. "This is something people have been focused on for quite some time, but we're all hopeful of strong clinical results in the near future."

SIGNS OF SCIENTIFIC EFFICACY

So how might developers go after multiple targets? Levine cites a paper by Anna Wing, Carl June, and colleagues from 2018 (1); their approach targets two antigens at once using both CAR T-cells and an oncolytic virus-driven bispecific antibody. "It's one of my favourite papers," says Levine, who worked with Carl June on developing the first CAR T-cell therapies. "Essentially, you get three for one; you have the two antigens targeted as well as the antigens released by the oncolytic vector."

With regard to synthetic biology, Levine highlights the integration of switch receptors. "This involves turning a negative signal into a positive," he explains. "You can make a switch receptor with PD-1, extracellularly, and then a signal-transducing co-stimulatory signal like CD-28. So when the tumor delivers a negative signal, the engineered T-cell sees it as a positive signal. That's really clever."

In April, the University of California San Francisco published two papers on their "SynNotch" system. In the first paper, they found that SynNotch-CAR-T cells could completely clear human patient-derived tumors from the brains of mice – safely and without recurrence (2). In a second paper, another set of researchers showed how components of the system can be switched out to target other cancers, such as ovarian and lung (3).

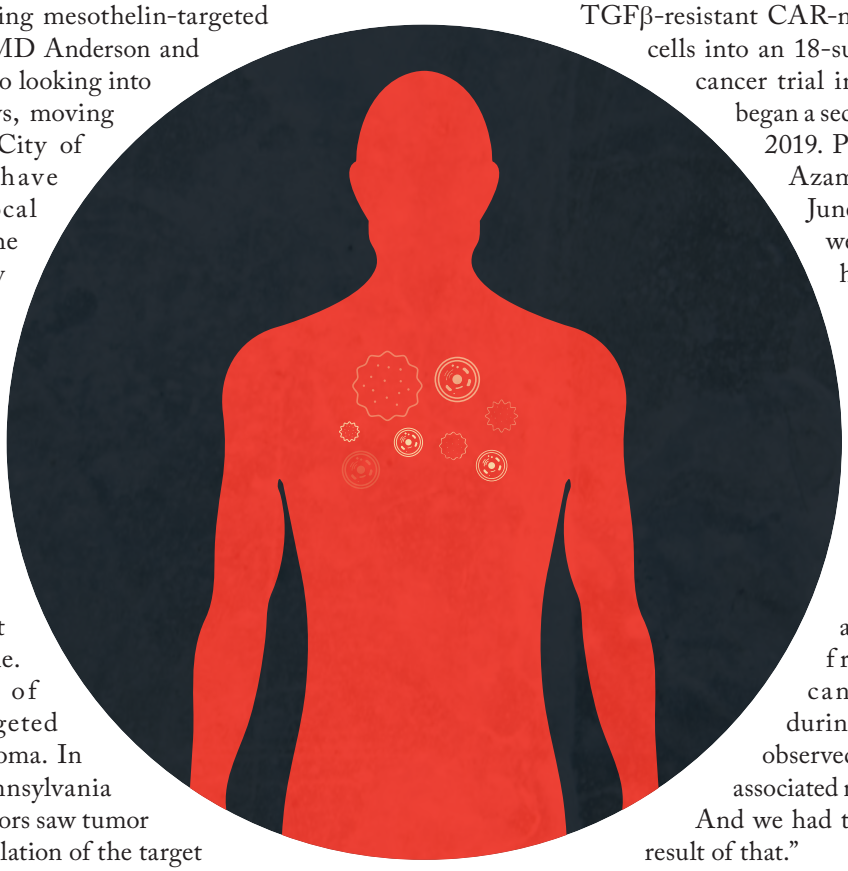
The new approach has two steps. The first step uses SynNotch to grant CAR Ts the ability to "judge" whether they are in a tumor. The second step uses a different set of SynNotch sensors to ensure a strong tumor-killing response. "Our approach allows us to prime the expression of the CAR against broad tumor antigens only in conditions where the T cells see tumor-specific or brain-specific signals," says Hideho Okada, co-author of the first paper. "As such, the SynNotch-T cells are safer and more effective."

Okada and his team are actively working on moving into the clinic. "We're also developing brain-specific priming," he says. "In the paper, we described priming by MOG, but there

"It's going to take a combination of strategies and targets, including synthetic biology."

may be other brain-specific antigens that may work as well."

Levine is also excited about local administration of CAR T-cell therapy. His team at the University of Pennsylvania are locally administering mesothelin-targeted CAR Ts to tumors. "MD Anderson and Sloan Kettering are also looking into this approach," he says, moving on to describe how City of Hope researchers have also incorporated local administration into the CNS. "That's technically challenging, but they did see some evidence of clinical efficacy." They've also used lentiviral transfer of CAR, targeting mesothelin. "We saw clinical activity in one-out-of-five pancreatic cancer patients using that approach," says Levine. UPenn and City of Hope have also targeted EGFRviii in glioblastoma. In the University of Pennsylvania clinical trial, investigators saw tumor necrosis and downregulation of the target in patient tumor tissue.



Another promising area is macrophage-based cell therapy. In 2020, University of Pennsylvania researchers genetically engineered macrophages to kill solid tumors in both mouse models and human samples (4). Then, in March 2021, Carisma Therapeutics – a company founded by researchers at the University of Pennsylvania – announced that it had dosed its first human participant in a phase I clinical study assessing the safety of CAR macrophages (5).

"Engineered macrophages may be particularly suited to the very challenging microenvironment of solid tumors," says Levine. In a review of recent developments in CAR-macrophage-based treatments for solid tumors from Anhui Medical University, China, researchers cited "great potential" when it came to migration to tumor and recruitment of immune effector cells (6).

However, a central challenge with engineered cell therapy is the potential for toxicity and cytokine release syndrome. Tmunity recently suffered a serious setback after the company was forced to shut down and modify their lead program for prostate cancer after two patients died following CAR T-cell therapy. The researchers had taken PSMA-specific and TGFβ-resistant CAR-modified autologous T cells into an 18-subject phase I prostate cancer trial in 2017. Tmunity then began a second, larger study late in 2019. President and CEO Oz Azam and co-founder Carl June explained that they were initially shocked at how well the therapy was performing in a recent interview with Endpoint News (7). But the two deaths in the small study forced a rethink.

"What we are discovering is that the cytokine profiles we see in solid tumors are completely different from hematologic cancers," said Azam, during the interview. "We observed immune effector cell-associated neurotoxicity – ICANS. And we had two patient deaths as a result of that."

"We didn't see this coming until it happened," said June. "But I think we'll engineer around just like we did with tocilizumab back in 2012."

"We've been lulled into a false sense of security by the rapid progress with blood cancers," says Levine. "But with solid tumors, while we're making progress – we have more centers working on the problem, as well as new tools and technologies – we're going to need long attention spans."

THE CAR ALTERNATIVES

Another set of promising non-CAR-based approaches to the development of solid tumor therapy involves T-cell receptors (TCRs). CAR technology uses an artificial receptor introduced into the immune effector cells to recognize tumor cell surface proteins (such as CD-19 or EGFRviii). In contrast, TCR-engineered effector cells use naturally occurring (or minimally modified) TCRs that have been selected for their ability to recognize tumor-specific epitopes presented by the major histocompatibility complex (MHC) molecules on the tumor cell surface.

"Here, you're targeting peptide fragments from intracellular targets expressed on the cell surface in the context of HLA, which only TCRs can address," says Norry, who has been actively researching this area alongside his colleagues at Adaptimmune. "This increases the number of potential targets and allows for greater specificity – you can more readily differentiate between cancer and healthy tissue."

Our T-cell receptors may be recognizing malignant cells all the time and destroying them without us ever realizing. Some malignant cells avoid this protective mechanism and become tumors. By enhancing the affinity of these receptors, researchers can give TCRs the ability to recognize a tumor as foreign – and then attack it.

In addition to enhancing the affinity of the T-cell receptor, researchers are also focused on improving the potency of T cells as a whole. "We and other groups are focusing on increasing the ability of T cells to overcome the inhibitory features of the tumor microenvironment," says Norry. "We've also shown, in a laboratory setting, that we can enhance their ability to recruit the rest of the immune system once activated."

The ability to recognize intracellular antigen fragments presented by MHC molecules increases the number of targets available to TCR therapies; however, it also makes the therapy "MHC restricted," which means their activity depends on presentation by MHC molecules to recognize targets and activate T cell functions. "This is a potential limitation because we all have our own MHC (or HLA) types – some are more or less common," says Norry. "This means that a given TCR may only work in a certain sub-population."

Norry and his team are developing TCRs that work across various HLA types. "We're also developing something called an HLA-independent TCR, which would expand the applicability of the therapy to a broader population."

Researchers from the MD Anderson Cancer Center recently reviewed the current technology and early clinical development of TCR-based therapy in patients with solid tumors, concluding that, while still early stage, TCR therapies may prove to be a "more effective option for solid tumors where intracellular antigens presented in MHC." The researchers also thought it "plausible" that TCR therapies could be cheaper, given the "substantially lower costs" associated with the manufacturing processes. However, Levine is skeptical of the costs being substantially lower. "I'm not aware of how this would be true for TCRs and not for CARs," he says.

"We're very optimistic about TCRs," says Norry. "We have a first-generation TCR in the clinic for patients with sarcoma,

Fabian Gerlinghaus

"But treating hundreds of thousands – or even millions – of patients using this relatively complicated, somewhat manual manufacturing process seems unlikely."

AUTOMATING CELL THERAPY MANUFACTURING

Fabian Gerlinghaus, Co-Founder and Chief Executive Officer at Cellares, believes he can make autologous cell therapy a realistic proposition for solid tumors by closing and automating manufacturing

How did you become interested in cell and gene therapies?

I originally trained as an aerospace engineer in Germany. I considered careers in aerospace or robotics, but when I went to the US I became fascinated with life-sciences and genetics. I ended up co-inventing an RNA synthesizer technology, which I then helped commercialize at Synthego, a leading genome editing company. We started with five employees in a garage and grew to more than 230 employees over the course of my five-year tenure. Later in my career I was attending a lot of conferences, and speakers would often talk about the challenges of commercial scale cell therapy manufacturing. In particular, I kept hearing that the industry needed closed and fully automated manufacturing technologies. We thought we could make a difference with our experience in inventing, developing and commercializing new bioprocessing technologies, so we set out to build the most advanced cell therapy manufacturing technology to accelerate access to life-saving cell therapies. This was the birth of Cellares.

How does your technology work?

We are fully automating and closing the entire cell therapy manufacturing process, to enable commercial scale manufacturing in a way that is cost-efficient, robust and scalable. Current cell therapy processes involve a plethora of different benchtop instruments, each with their own respective consumables. Everything is disjointed and made by different vendors. We're bringing it all together in an all-in-one single-use cartridge, which supports all of the unit operations end-to-end. The entire manufacturing process takes place in one closed tubing set, which itself, is contained within a secondary hard-shell that was designed with automation in mind. By closing and automating the process in this way – without compromising on process flexibility – we are radically reducing the risk of process failure due to contamination or operator error, while also pushing down costs.

Could closed and automated manufacturing tech benefit therapies for solid tumors?

We are looking at the prospect of treating hundreds of thousands of patients per year, per drug. Those kinds of numbers simply aren't possible with current manual processes. Our modular manufacturing platform, the Cell Shuttle, is essentially a factory in a box. It contains all of the required bioprocessing instruments inside a robotic workcell that maintains an ISO 7 cleanroom internally. Inside the Cell Shuttle, the robot moves single-use cartridges from one instrument to the next in accordance with the process you previously designed in software. Importantly, you can load 10 single-use cartridges and execute up to 10 autologous or allogeneic processes simultaneously. This is an order of magnitude improvement in throughput! By combining end-to-end automation with an order of magnitude improvement in instrument throughput, Cellares enables cell therapy manufacturers to meet commercial scale patient demand and overcome this manufacturing bottleneck. We're seeing that closed and automated technology can bring down manufacturing costs by up to 70 percent for autologous cell therapy manufacturing workflows. I genuinely believe our technology will benefit therapies for solid tumors by enabling cost-efficient manufacturing of hundreds of thousands of doses per year, per drug.

Where do you stand on the "allo versus auto" debate, particularly with regard to solid tumors?

I've discussed this question with our advisor, Carl June, and I think we're on the same page: there's going to be a place for both autologous and allogeneic cell therapies. Of course, one of the main drivers for allogeneic therapies is the autologous scalability issue. We think that closed and automated technology can shift the balance here by making autologous more scalable and cost-efficient.

Which therapy approaches do you think are most promising?

I will leave it to the clinical experts to comment on therapeutic approaches, however we are obviously impressed by those of our partners PACT Pharma and Poseida Therapeutics. PACT Pharma is working on neoTCR-T cell therapies, which I think have tremendous potential, and Poseida Therapeutics has a very strong pipeline with both autologous and allogeneic CAR T-cell therapies.

which we believe will become the first registered TCR-based therapy for solid tumors. We also have a next-generation TCR therapy in the clinic that incorporates a CD8-alpha cofactor, which enhances the killing capability of the product (giving it enhanced killer T-cell properties)."

In addition to TCR therapy, researchers are also interested in tumor-infiltrating lymphocyte (TIL) therapy, which involves harvesting infiltrated lymphocytes from tumors, then culturing and amplifying them in vitro, and finally infusing them back to treat patients.

"I remember listening to a talk by Steve Rosenberg about TILs in 1986," says Ting, who also recounted how Rosenberg isolated TILs from multiple mouse tumor models in 1982 – the first time in history. In fact, the earliest attempt at TIL therapy in the clinic goes back to 1988, in which a 60 percent objective response rate in metastatic melanoma was achieved. "Now they're being used to treat solid tumors in clinical trials."

Because TILs are composed of T cells with multiple TCR clones capable of recognizing an array of tumor antigens, a TIL-based approach may allow researchers to tackle tumor heterogeneity more easily than in CAR T and TCR T-cell therapy.

A recent review of TIL therapy for solid tumors found that there have been 79 trials of TIL therapy, including 22 kinds of TIL products between 2011 and 2020 – and factoring in two successful phase II trials by Iovance in 2018 (8). The researchers highlighted "impressive clinical benefits" in metastatic melanoma and advanced cervical cancer, even in patients treated with checkpoint inhibitors, while emphasizing that "the laborious, expensive, and time-consuming tissue collection and production process" means TILs are only currently being developed at a few leading research institutions and companies in a handful of countries.

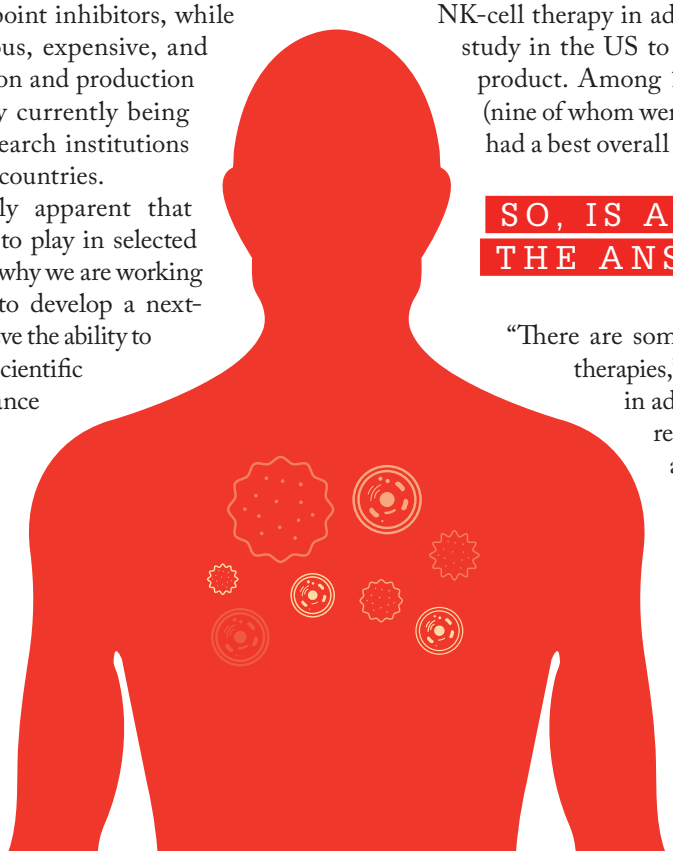
"It has become increasingly apparent that TIL therapies will have a role to play in selected indications," says Norry. "This is why we are working with the CCIT in Denmark to develop a next-generation TIL product. We believe the ability to modify TILs with our next-gen scientific capabilities to potentially enhance efficacy has great promise."

ALLO VERSUS AUTO

So far, the CAR T-cell therapies that have made it to the market have been autologous (the patient's own cells are taken out of their body, modified so they target cancer cells, and then reinjected). But treating hundreds of thousands – or even millions – of solid tumor cancer patients using this relatively complicated, somewhat manual manufacturing process seems unlikely. One alternative is allogeneic cell therapy – an off-the-shelf alternative in which donor cells (rather than the patient's own cells) are modified, which can reduce production time, cost, manufacturing delays, and dependence on the functional fitness of patient T cells.

The major downside of allogeneic cell therapy is the potential for graft-versus-host disease, and host allorejection. There are, however, several approaches to overcome or at least ameliorate this difficulty, such as the generation of TCR-deficient T cells using genome editing tools such as CRISPR/Cas9. Researchers are also evaluating repeated rounds of administration, using chemotherapy-resistant CAR T-cell or genetically eliminating key molecules governing CAR T-cell immunogenicity (9).

Besides T cells, other cells are also being explored to generate allogeneic cell therapies. Most commonly this applies to NK cells because of their potent cytotoxic anti-tumor activity and favorable safety profile. NK cells tend to possess a smaller risk of inducing GVHD because (as opposed to T cells) NK cells kill independently of MHC expression – though one of the ways by which NK cells kill is by sensing the absence of self MHC. In 2020, Fate Therapeutics announced encouraging preliminary phase I data for their iPSC-derived allogeneic NK-cell therapy in advanced solid tumors – the first study in the US to evaluate an iPSC-derived cell product. Among 15 heavily pre-treated patients (nine of whom were refractory to prior therapy), 11 had a best overall response of Stable Disease (10).



SO, IS ALLOGENEIC THE ANSWER?

"There are some great qualities to allogeneic therapies," says Levine. "They can be made in advance, stored in the freezer, and ready to go within days. And there are certainly patients from whom we cannot collect or generate enough quality CAR T or even CAR-NK cells for autologous cell therapy.

"But I think it's going to be both – I just can't see allo-therapies ever reaching the

Bruce Levine

potency of autologous therapies. For me, it's more a question of how these therapies will evolve together – because they aren't being developed independently of one another."

But Norry believes that allogeneic approaches are particularly exciting: "The product can be more consistent from patient to patient, and you have the ability to gene edit rather than using a viral vector to introduce a piece, or multiple pieces of genetic material into the cell.

"Really, all of the various iterations of TCR therapy can be made using an allogeneic platform, and we – alongside several other companies – are making good progress in the allogeneic space. Ultimately, it's about making a real difference to the patient and I think both allogeneic and autologous approaches can do that for solid tumors."

In the end, the successful approach may be something totally out of the box. "There's got to be a revolution," says Levine. "When we're thinking about autologous therapy: integrating automation for sure, but maybe even going beyond that and generating CAR T-cells in vivo. There are several companies – probably a dozen now – using viral vectors or nanoparticles to create CAR T-cells in the patients without having to extract, modify, and readminister."

Recently, researchers from Nanjing University generated CAR T-cells in vivo using AAV vectors carrying the CAR gene. This "AAV delivering CAR gene therapy" (ACG) resulted in tumor regression in a mouse model of human T-cell leukemia (11).

"Just look at the disruption we've seen in the vaccine field with the development of mRNA lipid nanoparticles," says Levine. "I think the in vivo approach has the potential for massive disruption, and we'll soon see clinical data from some of these therapies.

"When one looks at solid tumors, treating hundreds of thousands of patients with the current autologous manufacturing methods wouldn't be sustainable. I don't know how it's going to shake out, but I think we'll find out by the latter end of this decade."

References

1. *A Wing et al., "Improving CART-Cell Therapy of Solid Tumors with Oncolytic Virus–Driven Production of a Bispecific T-cell Engager," Can Imm Res, 6, 5 (2018). DOI: 10.1158/2326-6066.CIR-17-0314*
2. *JH Choe et al., "SynNotch-CAR T cells overcome challenges of specificity, heterogeneity, and persistence in treating glioblastoma," Sci Trans Med, 13, 591 (2021). DOI: 10.1126/scitranslmed.abe7378*
3. *A Hyrenius-Wittsten et al., "SynNotch CAR circuits enhance solid tumor recognition and promote persistent antitumor activity in mouse models," Sci Trans Med, 13, 591 (2021). DOI: 10.1126/scitranslmed.abd8836*
4. *M Klichinsky et al., "Human chimeric antigen receptor macrophages for cancer immunotherapy," Nat Biot, 38, 947-953 (2020). DOI: 10.1038/s41587-020-0462-y*
5. *PR Newswire, "CARISMA Therapeutics to Present Data at The American Association for Cancer Research Annual Meeting" (2021). Available at: https://prn.to/3bTkh68*
6. *Y Chen et al., "CAR-macrophage: A new immunotherapy candidate against solid tumors" (2021). Available at: https://bit.ly/2RRto0r*
7. *Endpoints (2021). Available at: https://bit.ly/3vWdHTI*
8. *S Wang et al., "Perspectives of tumor-infiltrating lymphocyte treatment in solid tumors," BMC Med, 19, 140 (2021). DOI: 10.1186/s12916-021-02006-4*
9. *DM Beoya, V Dutoit and Migliorini, "Allogeneic CAR T Cells: An Alternative to Overcome Challenges of CAR T Cell Therapy in Glioblastoma," Front Immunol (2021). DOI: 10.3389/fimmu.2021.640082*
10. *Fate Therapeutics (2020). Available at: https://bit.ly/3BsHibp*
11. *W Nawaz et al, "AAV-mediated in vivo CAR gene therapy for targeting human T-cell leukemia," Blood Can J, 11, 119 (2021). DOI: 10.1038/s41408-021-00508-1*

THE CELL + GENE CURATOR

A roundup of the key solid tumor CGT stories from 2021 so far, taken from our weekly newsletter: The Cell + Gene Curator.

January

- Strand Therapeutics and BeiGene enter into agreement to develop mRNA-based treatments for solid tumors
- Merck secures licenses for up to three of Artiva Biotherapeutics' allogeneic CAR-NK cell therapies targeting solid tumors, with Artiva set to receive $30 million upfront and up to $612 million per program in milestone payments
- Queen Mary University of London team identify CEACAM7 as potential target in pancreatic ductal adenocarcinoma and use CEACAM7-targeted CAR T-cells to mediate remission in patient-derived xenograft tumors
- In the quest to fine-tune CAR T cell therapy, researchers from the Dana-Farber Cancer Institute have created a switchable CAR T cell that can be turned on or off with lenalidomide
- Kite will evaluate new cell therapies for solid tumors and hematologic malignancies using five targets identified by Oxford BioTherapeutics' OGAP discovery platform as part of a new collaboration

February

- Guangxi Medical University researchers use CRISPR to design nanobody-based anti-CD105 CAR T-cells for solid tumors that prolong the survival time of tumor-bearing NOD/SCID mice
- Minaris will manufacture, freeze, and ship MaxiVAX's MVX-ONCO-2 capsules – a cell-based immunotherapy for solid tumors – as part of partnership

March

- Wugen will manufacture, develop, and commercialize Shanghai-based Alpha Biopharma's allogeneic memory NK and CAR T cells for solid tumors as part of license and collaboration agreement
- Carl June and colleagues describe methods for activation, expansion, and characterization of human CRISPR-engineered CD19 directed CAR T cells
- Pasteur Institute researchers find that cross-talk between CAR T cells and tumor microenvironment is necessary for optimal CAR T cell efficacy

April

- Chinese Academy of Sciences team use indocyanine green nanoparticles to modulate tumor microenvironment and robustly boost CAR T in solid tumor models
- Transient disruption of CAR signaling or "rest" reinvigorates exhausted CAR T-cells and boosts anti-tumor functionality in mouse models, according to researchers from Stanford University School of Medicine
- Carisma establishes a multi-year collaboration with Bruce Blazar from the University of Minnesota to investigate and develop allogeneic macrophage therapies

Queen Mary University of London Image by Matt Brown

May

- Athenex to acquire Kuur Therapeutics and its allogeneic CAR-NKT technology for $70 million upfront and $115 million in development milestones
- Prescient Therapeutics will collaborate with Peter MacCallum Cancer Centre to develop "next generation" CAR-T products using Prescient's OmniCAR technology for AML and solid tumors
- MD Anderson and Refuge Biotechnologies are working together on engineered TILs and CAR T-cell therapies for solid tumors. MD Anderson will apply Refuge's cell engineering platform to its TIL programs, and

the companies will co-develop Refuge's RB-340, a HER-2 targeted CAR T.

- Imugene licenses City of Hope's CD19-expressing oncolytic virus (see research below), aiming to unlock CD19-directed CAR T-cell therapies for solid tumors
- City of Hope combine their oncolytic virus expressing IL-15/IL-15Rα with allogeneic EGFR-CAR NK cells and inhibit growth of glioblastomas in mice

June

- ONK Therapeutics teams up with Trinity College Dublin to optimize the metabolism and engineering of NK cells for solid tumor cancers
- Inceptor Bio raises $26 million to advance multiple cell therapy platforms – including CAR-T, CAR-M, and NK/NKT – to treat cancer by focusing on enhancing cell performance in tumor microenvironment
- Peter MacCallum Cancer Centre spinout Currus Biologics grabs $10 million in Series A funding to combine its Bispecific Engagers of Antigen Presenting Cells and T cells (BEAT) technology with CAR-T therapy to treat solid tumors
- HER2 CAR-NK cells from both healthy donors and patients with breast cancer exhibit enhanced cytotoxicity and IFN-g production against HER2-expressing breast and ovarian cancer cells in vitro

July

- Inceptor Bio launches Fastback Bio with technology licensed from University of North Carolina at Chapel Hill to develop CAR T-cell therapies for solid tumors
- Genocea doses first solid tumor patient in phase I/IIa clinical trial for neoantigen-targeted T cell therapy GEN-011
- At Capital Medical University, Beijing, researchers find that autologous invariant natural killer T cell administration is safe and well-tolerated in patients with hepatocellular carcinoma
- Seattle Children's researchers engineer medium-length CAR spacer to enhance efficacy of HER2-specific CAR-T cells in orthotopic xenograft medulloblastoma model

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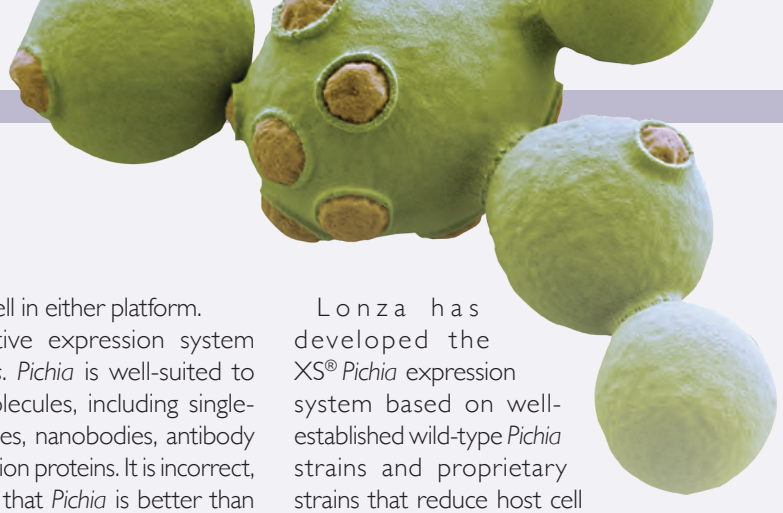


A Matter of Expression

Lonza and Cytena combine expertise to allow biotherapeutic manufacturers to benefit from the advantages of *Pichia pastoris* as an expression system

By Joachim Klein and Julian Riba

Speed to market is important for both manufacturers and patients. For some companies, the pressure to reach commercialization as quickly as possible leads to a temptation to rush early-stage development. But it is crucial to make the right decisions early on to avoid problems during scale-up – and the need to go back and make changes and corrections. One common mistake is to use an unsuitable expression system and starting strain, which then turns out to be unviable for commercial-scale yields for that molecule. Although mammalian and *E. coli* expression systems are the traditional workhorses for biomolecules, there is an increasing trend towards more complex biotherapeutics that cannot always be expressed well in either platform.

One alternative expression system is *Pichia pastoris*. *Pichia* is well-suited to complex biomolecules, including single-domain antibodies, nanobodies, antibody mimetics, and fusion proteins. It is incorrect, however, to say that *Pichia* is better than mammalian or *E. coli* – it all comes down to what is best for the molecule. It's important to take the time to conduct product screening to choose the right expression system (and, in the case of *Pichia* and mammalian, the right clone) for your molecule and perform the necessary tests if you want to increase the chances of success for your project. Each molecule is different. And just because you have always used CHO doesn't mean it is the best system for your new molecule. Why not look more closely at what other systems could do?

New horizons for *Pichia*

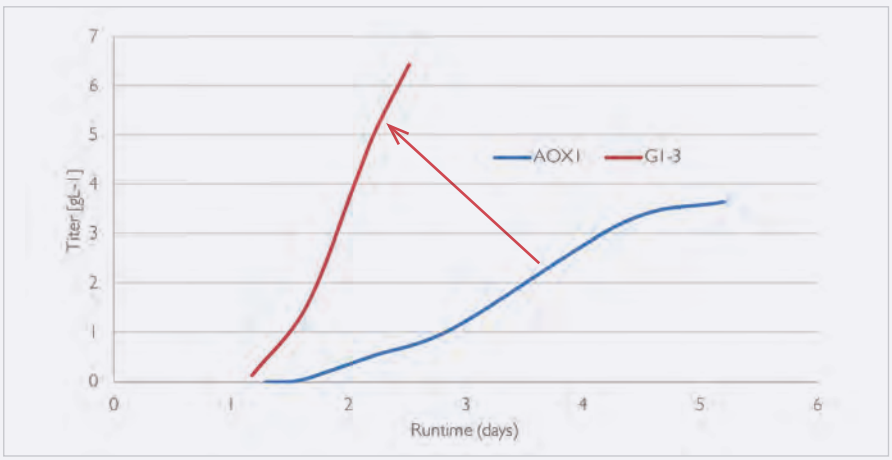
Pichia is not new, and drugs expressed in *Pichia* are already available on the market. There are some huge benefits to using *Pichia*. It produces very pure protein with no endotoxin and no viral clearance is required. *Pichia* is also a eukaryotic host organism, which makes it better at folding and assembling complex proteins into functional molecules.

Lonza has developed the XS® *Pichia* expression system based on well-established wild-type *Pichia* strains and proprietary strains that reduce host cell impurities. Co-expressed helper factors can also be used to maximize productivity. Methanol (AOX1) and constitutive promoter systems can be used with XS® *Pichia* if customers wish, but Lonza has also developed an alternative: a proprietary glucose fed-batch strategy. With Lonza's Glucose Regulated Promoters (G1-3), fermentation can be designed faster in bacterial-like fermentation times than when using methanol because of a more favourable correlation between growth rate and specific protein production rate. Additionally, G1-3 eliminates other apparent drawbacks of the traditional methanol induced AOX1 system, which is not easy to scale up, and requires highly specialized handling procedures and explosion-proof facilities.

Combined expertise

As noted above, to get the most out of *Pichia*, it is essential to select the right clone – but the screening process can be challenging. Lonza has clear expertise in expression systems and Cytena has expertise in developing patented instruments for controlling individual cells – and the combination led to an inevitable partnership that smooths the road for manufacturers.

In more detail, Cytena's B.SIGHT™ single-cell sorter can be used for automated single-cell cloning of Lonza's XS® *Pichia* strain to help to identify the best cell line development option. This allows to screen hundreds or even thousands of clones automatically!



The G1-3 Glucose Regulated system reaches a much higher titer in a shorter time frame than traditional methanol based systems.

Lonza Biologics

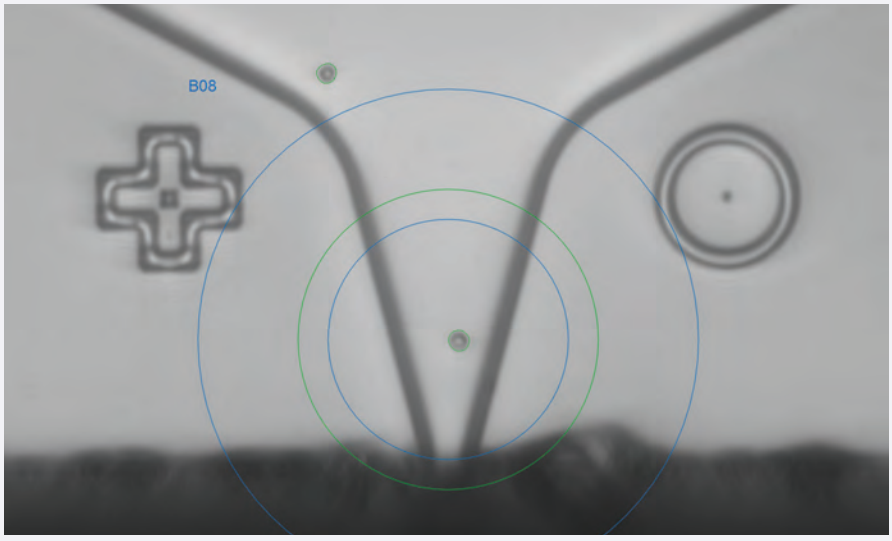
This represents significant progress when you consider that clone selection is typically conducted using solid media plates dependent on anabolic selection and auxotrophic markers, followed by picking of single colonies. Certainly, the traditional approach works, but it is time-consuming – a reality that limits how many clones can be screened. Why is that important? The quality of the selected best performing clones is dependent on the number of clones generated – the more clones you screen, the higher the likelihood of finding a high-producing clone.

Cytena's single-cell dispensers are well-established for the development of mammalian producer cell lines, but the company has also turned its attention to automated isolation for microorganisms, such as *E. coli* and yeast strains, including *Pichia*. Methods for cloning microorganisms have perhaps lagged behind the development of cloning methods for mammalian cells because working with microorganisms is more challenging due to their smaller size, which makes optical detection and single-cell handling more challenging. Traditional methods, such as limiting dilution or streaking on agar, can be used, but they don't guarantee that the resulting colonies are indeed clonal – and they typically result in rather complex workflows. Limiting dilution results in a lot of empty wells and, after bringing cells onto agar, they must at some point be brought back to liquid media. Cytena's B.SIGHT single-cell dispenser automates the process and everything is performed fully in liquid culture without labels – and within a very small footprint.

An automated future awaits

There is no doubt that the future lies in automation; there is increasing demand from customers for automated, accessible solutions that facilitate high-throughput biology. The collaboration between Lonza and Cytena will make *Pichia* much more accessible to labs – particularly small-to-medium laboratories that have previously lacked the capabilities to explore *Pichia* as an expression system and perform head-to-head analyses to really determine the best system for making the molecule.

Getting the best expression system early on means higher titers, easier scale-up, and, ultimately, an increased chance of getting your molecule to patients faster.



Cytena B.SIGHT™ single-cell sorter dispensing XS® Pichia clones into a 96 well plate.

The Experts

Joachim Klein, Head of Microbial Strain Development and Cell Banking, Lonza Biologics

"Lonza is a go-to company for commercial production. Mostly recently, we have been involved with the production of the Moderna vaccine. I have been with the company for over 20 years and, in my group, we focus on microbial development – developing viable production strains for large-scale manufacturing for biotherapeutics of interest. This is not a simple task because you cannot predict what production host is best and what problems you face; testing is essential.

"We have been developing Lonza's XS® *Pichia* technology since its inception – and even before then, we were very interested in Pichia's potential. I believe that our platform addresses all of the issues associated with the AOX1 *Pichia* methodology and now it is available to take it to your labs via our licensed option."

Julian Riba, CEO, Cytena

"Cytena started out as a spinoff from the University of Freiburg in 2014. Today, our single-cell dispensing technology is used by most of the top 20 pharma companies for the development of mammalian producer cell lines. During my PhD I pioneered single-cell dispensing of bacteria which was the basis for the development of the B.SIGHT at Cytena."

NextGen

R&D pipeline
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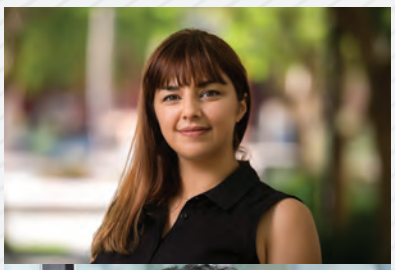
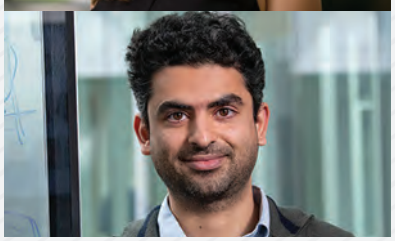
AI Reunites Pharma with Mother Nature

Can AI facilitate a grand comeback for medicines sourced from Mother Nature?

By Angus Stewart and Stephanie Sutton

Meet the Researchers





Bahar Behsaz and Hosein Mohimani both work at the Computational Biology Department in the School of Computer Science at Carnegie Mellon University, Pittsburgh, Pennsylvania, USA.
Bahar is a Project Scientist and Hosein Mohimani is an Assistant Professor.

Many popular therapeutics have come from nature, but with the low-hanging fruit taken and new discoveries in the field becoming increasingly challenging, big pharma began to look to other sources of new drugs, effectively severing the original branch of medical discovery for small molecules. But not all that is abandoned need be forgotten – as proven by work undertaken in Carnegie Mellon University's Computational Biology Department, which could accelerate a "return to the future" of novel natural product research.

We sat down with two of the involved researchers – Bahar Behsaz and Hosein Mohimani – to hear how they used an AI platform to identify molecules that could open up new avenues in small molecule discovery.

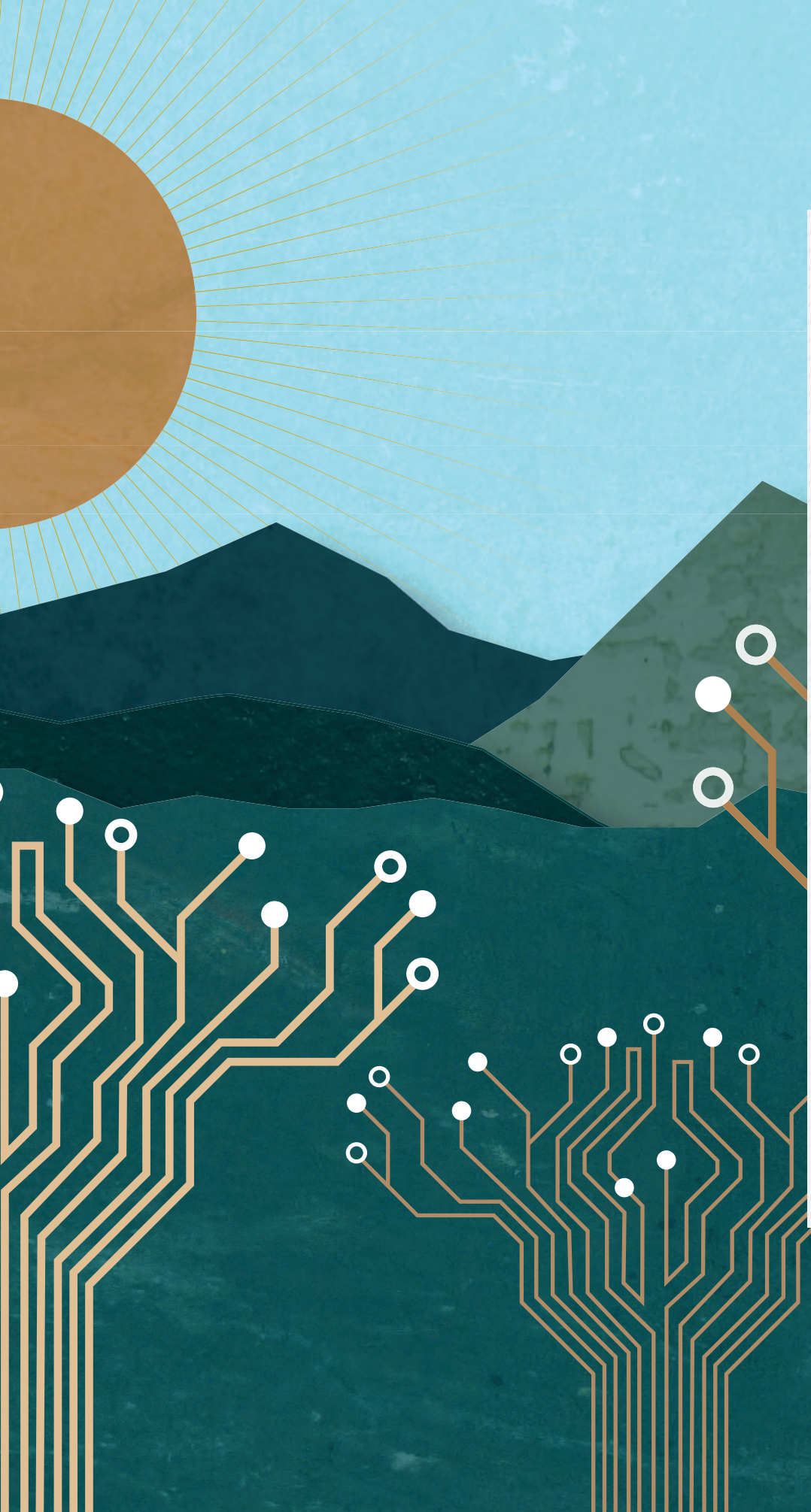
What are your research interests?

We focus on developing cutting-edge technologies for discovering new drug leads from nature. We focus on a class of molecules called natural products. These molecules were naturally selected across millions of years of evolution to carry a very wide range of bioactivities, which makes them a generous source of drug discovery. We're specifically interested in developing computational methods that integrate a range of biological Big Data to identify drug-like natural product molecules. In the past, much of our research focused on identifying known molecules – but, today, we have pushed the technology further and are focusing on scalable methods that can discover completely new small molecule compounds with no known counterparts.

What was the motivation behind your research?

Approximately half of all existing clinically approved drugs are inspired by nature. This includes most antibiotics and many widely used antitumor medications. Take penicillin, for example; it is among the most used and well-known natural product drugs, and was discovered – accidentally – by Alexander Fleming when he left a Petri dish uncovered overnight. Most natural products were discovered either by luck or through complex, time- and labor-intensive trial-and-error experiments. It often takes years and millions of dollars to make a single discovery.

By the early 1990s, major pharmaceutical companies had mostly abandoned the search for new natural



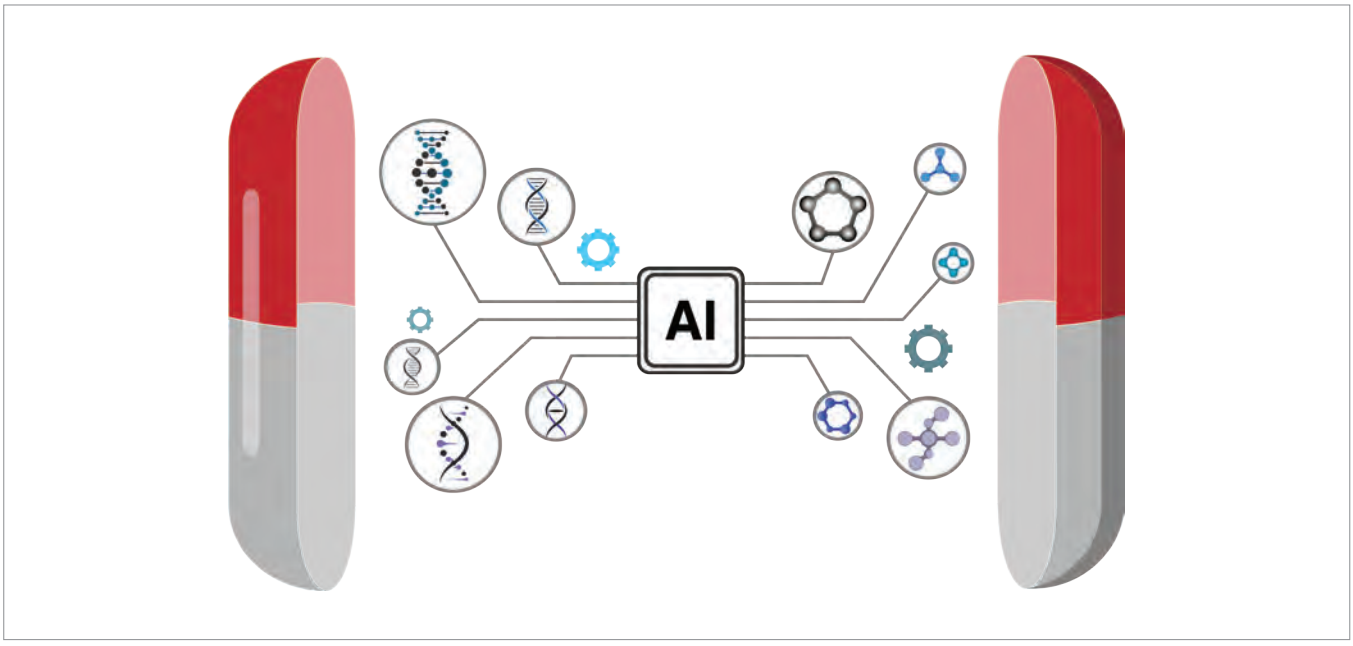
The Work

Behsaz and colleagues have developed a modification-tolerant tool called NRPminer that can identify NRPs from (meta)genomics and mass spectrometry databases. The tool can mine NRPS from different environments, including four previously unreported NRP families from soil-associated microbes and human microbiota.

NRPs are produced by metabolic pathways encoded by biosynthetic gene clusters (BGCs). Genome mining tools are available that can predict potentially therapeutic NRPs produced by a given BGC, but there is a challenge. According to the researchers, "it remains unclear which of these putative NRPs is correct and how to identify post-assembly modifications of amino acids in these NRPs in a blind mode, without knowing which modifications exist in the sample."

NRPminer can predict the amino acid sequence of an NRP produced by a BGC, analyze non-canonical assembly lines, and predict potential post-assembly modifications and backbone structures.

Read more in the research paper: B Behsaz et al., "Integrating genomics and metabolomics for scalable non-ribosomal peptide discovery", Nature, 12, 3225 (2021). DOI: 10.1038/s41467-021-23502-4.



products. Today, access to high-throughput omics data provides a new roadmap for scalable natural product discovery, but this is only possible if we have computational methods that can use this massive data.

What were your key findings?

We presented a new platform (NRPminer) that combines the power of two different omics technologies – genomics and metabolomics – to discover new natural products at scale (1). The machine learning algorithms we have developed automatically match the signals of a microbe's metabolites with its genomic data, then identify signals that correspond to a new natural product. This provides researchers with the crucial information they need to isolate the natural products and begin developing them for clinical trials. The method is scalable and can work automatically across thousands of microbial samples.

We further demonstrated that our approach can identify many novel natural products generated in different environments. In particular, we presented four completely novel families of molecules from soil-associated microbes and human skin microbiota. We have demonstrated the antiparasitic activities of two of these non-ribosomal peptide families using direct bioactivity screening, illustrating the strength of our method for discovering novel drug leads.

What's next for this project?

We are currently applying our integrative methods to even more diverse classes of natural products with different functionalities, and we are creating more methods that are suitable for commercial-scale lead drug discovery.

In your view, does pharma make the most of machine learning for drug discovery?

AI is certainly a staple in today's pharmaceutical research and development. In the past decade, we have observed more and more companies focusing on the use of AI and machine learning. The most commonly deployed methods focus on prediction of activity, drug design, repurposing, and testing drugs.

Parallel to that, the past decade saw significant advances in high-throughput omics technologies, which opened up a range of new opportunities. In accordance with these experimental advances, scalable computational platforms are emerging. These could enrich all discovery efforts tapping into novel natural products – a completely new space of unexplored small molecules with stunning structural and functional diversity. Scientific progress is now at the stage where – as we demonstrated – it is possible to apply large-scale methods of natural product discovery at the commercial level.

It is not surprising that we are now seeing big pharma shift to a clear focus on natural products for discovering novel drug leads. We are confident that this is just the beginning of the resurgence of natural products, enabled by scalable machine learning and data mining methods.

Through various examples, we have demonstrated the methods that can mine this untapped goldmine. Current AI technologies can provide pharmaceutical researchers with crucial information about new compounds and their potential as valuable drug leads. This would provide an opportunity to tackle currently untreatable diseases.

Reference

1. *B Behsaz et al., "Integrating genomics and metabolomics for scalable non-ribosomal peptide discovery", Nature, 12, 3225 (2021). DOI: 10.1038/s41467-021-23502-4.*

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Business

Economic drivers
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What Lies Ahead for Biosimilars?

The advent of biosimilars promises to make the world a healthier place by bringing more affordable biologic medicines to patients in need

It's been 15 years since the launch of the world's first biosimilar (Omnitrope – a biosimilar recombinant human growth hormone), but have biosimilars been flooding the marketplace ever since? In some countries, uptake is high, but in others the innovator biologic remains the most popular option. In fact, several obstacles lie in the way of increasing biosimilar usage, including education and regulation.

Here, we speak with Pierre Bourdage, Global Head of Biopharmaceuticals at Sandoz, to find out how well biosimilars are faring – and how uptake can be boosted to benefit patients.

Where are biosimilars winning?

It has been fifteen years since Sandoz launched the world's first biosimilar. Since 2006, we have seen how biosimilars have transformed patient lives, improving access to potentially life-changing medicines for people with chronic and debilitating conditions and by contributing substantially towards healthcare sustainability. In Europe alone, the total clinical experience with biosimilar medicine exceeds two billion patient treatment days (1). Take Bavaria in Germany, for example; prior to the launch of the first biosimilar approved for rheumatoid arthritis (RA), patients had to wait 7.4 years to be treated with a biologic. Following the introduction of biosimilars in this space, the waiting time is now down to two or three months (2).

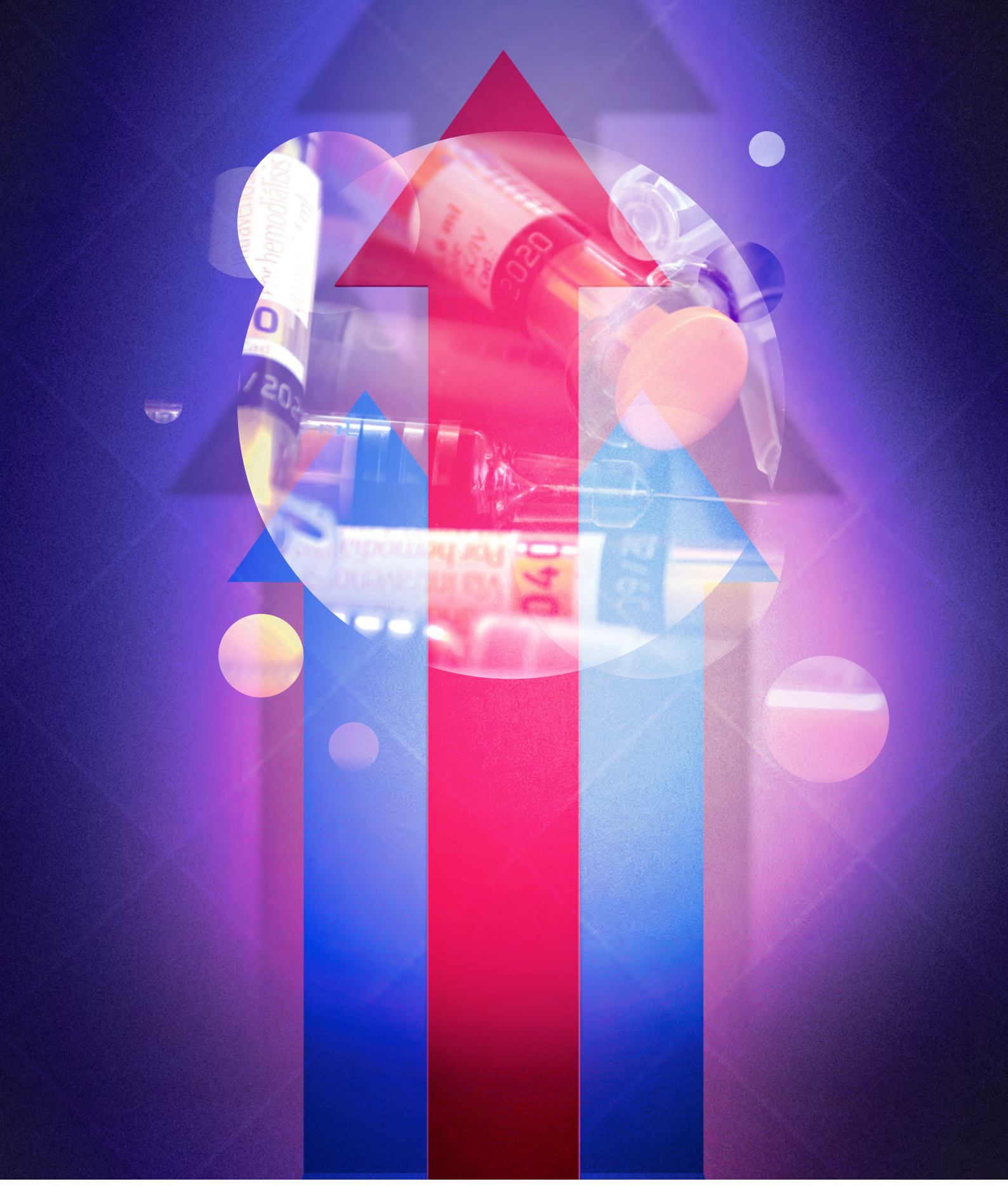
Spain – from 2009 to 2020 – presents another good demonstration of falling costs; cancer and inflammatory therapy areas generated savings of €2.4 billion thanks to the entry of biosimilars (2).

In Australia, a very recent report found that the Austrian healthcare system saved €700 million over the past 12 years; however, 71 percent of the market potential has still not been utilized.

In Italy, the hematology unit of a hospital saved 45 percent by switching to biosimilars in one year, with absolute savings of approximately €400,000 (3).

Encouraged by the substantial cost savings generated by biosimilars, the UK's National Institute for Health and Care and Excellence (NICE) recently released access guidance on the use of biologics. In addition to people with

"Since 2006, we have seen how biosimilars have transformed patient lives."



severe RA, people with moderate RA can now access biologics as well. This announcement has been a big breakthrough that could increase patient access to tens of thousands of people with moderate RA.

It's apparent that, over the years, biosimilars have demonstrated clear and meaningful benefits for patients and healthcare systems alike. But an area one hears less about is innovation. Biosimilars stimulate competition, which provides an incentive to continue developing novel products as biosimilar alternatives become more readily available for biologics currently on the market. Indeed, biosimilars can spark incremental innovations that benefit other stakeholders. These innovations can include improvements such as smaller needle gauges, new devices to make injections easier, new support services to best meet patients' needs, and medicines that can remain unrefrigerated for longer periods of time, which allows patients to take their medicine during travel and holidays.

Though Europe has led the way – approving more treatments than anywhere else on the globe – we are now starting to see traction in other countries too, including the US, Canada, and Japan, which are at varying stages of biosimilar adoption. We still have a long way to go before we can say we have truly unlocked the full potential of biosimilars and we should now focus on accelerating the adoption of biosimilars to the next level.

The healthcare systems of those countries that have successfully laid down infrastructure and incentives for the adoption of biosimilars – like Germany and UK – have done tremendously well. If we look at the Nordic countries like Denmark, we have seen adoption rates for biosimilars in treating immunologic diseases ranging from 85 to 97 percent. We have also seen a lot of support from government and regulatory authorities. In France, for instance, the government has set up an initiative to increase biosimilar penetration to 80 percent by 2022, although more needs to be done to achieve that.

The European Commission is driving the "Pharmaceutical Strategy for Europe" which aims to ensure access to medicines and support innovation and sustainability in the industry. The EU also aims to drive significant reforms including the improvement of regulatory efficiency and allowing generics/biosimilars to enter the market on day one of the expiry of the exclusivity period. Beyond these, some of the additional key factors that we can safely say have contributed towards the overall success of biosimilars in Europe include:

- A clear regulatory pathway for the entry of biosimilars from the EMA, which has played a crucial role in the introduction of biosimilars.
- Faster market access at a country level, with clear pricing and reimbursement rules – although this varies across countries.
- Increasing acceptance of patients and healthcare providers in therapeutic areas where biosimilars are more prominent.

What are some of the factors affecting uptake in different parts of Europe?

In Europe, a legal framework for the market authorization of biosimilars was established in 2004. Biosimilars are approved via stringent regulatory pathways by the same authorities that approve reference medicines and are developed using the same quality standards as reference medicines (4,5). After granting market authorization at the European level, local implementation is up to individual member states.

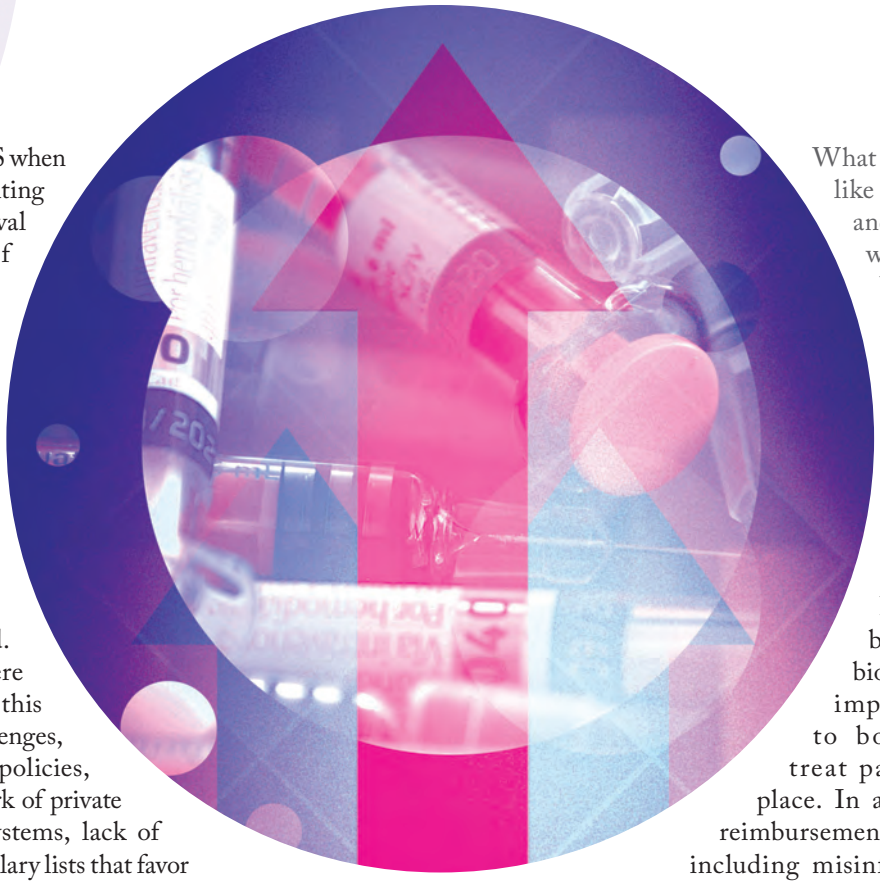
"Regulatory, reimbursement and other barriers, including misinformation, continue to delay access to biosimilars."

Consequently, each country can formulate its own biosimilar policies. Differences exist in the pricing and reimbursement procedures, levels of education, characteristics of covered population, and incentivization of stakeholders. This leads to variations in the adoption of biosimilars and divergences in savings from biosimilar use across Europe, and eventually even within the same country (6). There are also differences across therapeutic areas, as well as in the level of competition between reference biologics and biosimilars.

There is much that still needs to be done in order to move forward. In Poland, for example, only one percent of the eligible patients get access to a biologic for treating immunologic diseases (7) – a significant gap that biosimilars can help fill.

In the US, biosimilars are more recent and there are specific challenges in the market. Why did the introduction of biosimilars to the US take so long?

It's true that we have seen a lag when it comes to the launch of biosimilars in the US. I would say Europe is roughly a



decade ahead of the US when it comes to implementing frameworks for approval and marketing of biosimilars. There are more than 60 biosimilars currently approved across Europe – 16 of which are reference medicines. As of June 1, 2021, the FDA had approved 29 biosimilars in the US; 20 of which have been launched. In my opinion, there are many reasons for this lag: commercial challenges, lack of supporting policies, the complex patchwork of private and public health systems, lack of reimbursement, formulary lists that favor reference products (8), and finally, little awareness and miseducation on the value and clinical benefits of biosimilars (9).

That said, we are seeing that some progress has been made since the first US biosimilar approval under the Biologics Price Competition and Innovation Act pathway. Adoption of biosimilars has translated into savings for the US healthcare systems. Take Kaiser Permanente as an example; this integrated healthcare network has saved more than $200 million since 2015 by adopting biosimilars. It then reinvested these savings into improving patient access and care (10).

We are also pleased to see the US Congress taking steps to help improve patient and provider awareness of the benefits of biosimilars. One example is the introduction of the Advancing Education on Biosimilars Act. This is a new law that calls for the establishment of a website and the development of educational materials, to help bolster understanding of the terminology and standards related to regulatory approval and licensing of biologic products, biosimilars, and interchangeable biological products.

Is there also a problem with litigation and bad players intentionally trying to keep competitors out of the market?

Life science companies depend on intellectual property rights to drive and fund innovation. Sandoz respects valid intellectual property while also challenging patents that we think should not prevent the launch of biosimilars. For decades, Sandoz's commitment to challenging patents has driven access to affordable and high quality biosimilars for patients around the world. We will always give our best to speed access to biosimilars – but that does not mean we win every single time. Both Sandoz and Novartis believe that all parties to litigation regarding biosimilars should do all they can to ensure timely resolution of that litigation.

What changes would you like to see in the US – and elsewhere in the world – to increase biosimilar uptake?

There are changes that can definitely help unlock the potential of biosimilars for healthcare systems and patients in the US and across the globe. Improved access to biologics (including biosimilars) starts with improving capabilities to both diagnose and treat patients in the first place. In addition, regulatory, reimbursement and other barriers, including misinformation, continue to delay access to biosimilars and tie up limited resources. I believe there is an ardent need to focus on the following areas to increase adoption of biosimilars:

Improve awareness and understanding of the value of biosimilars among physicians and patients (especially in the therapeutic areas that new biosimilars will soon start to enter).

Fight misinformation about biosimilars. Healthcare providers and patients must believe in and receive honest, truthful information that builds their trust in biosimilars.

Adopt policies that incentivize the use of biosimilars, while making sure to stimulate long-term sustainability of the market (gain sharing, allowing multi-winner tenders, criteria beyond price that values quality, supply sustainability, and services to patients and clinicians).

Streamline reimbursement mechanisms and bureaucratic measures to accelerate biosimilar adoption from day one.

In the US, there are also certain additional policies that can help; for example, authorizing a temporary add-on payment to healthcare providers in Medicare Part B to increase prescription and use of biosimilars (as opposed to the current system, which encourages prescribing the most expensive option), and including biosimilars in the formularies of all Medicare Advantage and Part D plans without burdensome administrative and financial obstacles.

How big is the perception problem when it comes to biosimilars?

It's certainly a barrier that we must still overcome. Healthcare professionals play a significant role in biosimilar adoption. They are responsible for identifying the most appropriate treatment options and for discussing these options with their patients, enabling them to make an informed choice.

A recent literature review found that both US and EU physicians were largely unaware of biosimilars as safe and effective treatment options, despite plenty of evidence demonstrating that biosimilars are safe and effective, with no interruption to therapeutic outcomes upon switching (11-13).

Patient awareness and understanding of biosimilars is low, with only 6 percent of patients surveyed in the EU and the US being aware of biosimilars, and less than a third of patients in advocacy groups (15). Without adequate support from an informed healthcare professional, patients may resist switching from their existing treatment (a reference biologic) to a biosimilar medicine because they fear a compromise in safety and quality. Patients are going to have questions if their therapies are changed, so it is beneficial to have a straightforward

"Europe has been a key driver for our success, creating a clear biosimilar approval pathway and providing a leading example for other markets."

dialogue and answer their top five or ten questions.

The most salient educational message for all stakeholders is that an approved biosimilar is expected to match the reference biologic in terms of safety and efficacy with no clinically meaningful differences (15, 16). Furthermore, biosimilars are approved by the same regulatory authorities and manufactured to the same high-quality standards as reference biologic medicines (13,17).

There have been significant strides toward bridging the gap in biosimilar adoption, with plenty of tools and resources available. In Europe, the EMA has taken the lead on biosimilars education by providing comprehensive information guides for patients and healthcare professionals.

As we see an increasing number of biologics coming off-patent in newer therapy areas like multiple sclerosis and ophthalmology, we need to make early efforts to lay the groundwork for the acceptance of biosimilars through robust education programs that can help combat misinformation and disparagement campaigns.

Can you share Sandoz's journey so far?

Sandoz started the world's first biosimilar development program in 1996 and was the first pharmaceutical company to receive biosimilar approval in Europe, Japan, Canada, and the US. From the outset, we had full confidence in the potential of these medicines and the benefits that they could bring to both patients and healthcare systems.

In the early years, adoption was slow. However, with every new biosimilar, we are seeing an acceleration, as stakeholders learn from previous launches and build on existing policies. Europe has been a key driver for our success, creating a clear biosimilar approval pathway and providing a leading example for other markets.

In terms of the development and launch of biosimilars, is there sufficient variety?

Over the next 10–15 years, many biologics will come off-patent – in numbers we have never seen before. And that can only lead to further biosimilar competition in existing and new therapy areas. We believe this provides a great opportunity for biosimilars to deliver even more benefits for both patients and healthcare systems.

Our research and development efforts are focused on areas of unmet needs, and we are moving into a broader set of therapy areas. Furthermore, we have a pipeline of over 15 molecules, with plans to add at least one molecule per year.

References

1. *Medicines For Europe, "The total clinical experience with biosimilar medicines exceeds 2 billion patient treatment days" (2020). Available at: https://bit.ly/3rlhCIV*
2. *ProBiosimilars, "New study shows: Rheumatoid patients have faster access to biological therapy since biosimilars exist" (2020). Available at: https://bit.ly/3zbWE1R*
3. *Eversana, "Biosimilars Saved Spain 2,400 Million Euros Between 2009 and 2020," (2020). Available at: https://bit.ly/3xS3Xvh*
4. *DC Baumgart et al., Front Pharmacol., (2019). DOI: 10.3389/fphar.2019.00279*
5. *FDA, "How Drugs are Developed and Approved," (2019). Available at: https://bit.ly/3xPEVNn*
6. *EMA, "Biosimilar medicines: overview," (2019). Available at: https://bit.ly/2UpcaZz*
7. *MA Urru et al., Scientific Reports, 11 (2021). DOI: 10.1038/s41598-021-85563-1*
8. *A Vulto et al., PLoS ONE, "Policies for biosimilar uptake in Europe: An overview" ((2017). DOI: 10.1371/journal.pone.0190147*
9. *AJMC, The Center for Biosimilars, "What Are the Barriers to Biosimilar Uptake in the US?" (2020). Available at: https://bit.ly/3kzhiVQ*
10. *AJMC, The Center for Biosimilars, "How Kaiser Permanente Got Biosimilars Into Play," (2020). Available at: https://bit.ly/3zaq1BG*
11. *E Wolff-Holz et al., BioDrugs, 33, 621–634 (2019). DOI: 10.1007/s40259-019-00377-y*
12. *L Barbier et al., Clinical Pharmacology & Therapeutics, (2020). DOI: 10.1002/cpt.1836*
13. *E Leonard et al., J Manag Care Spec Pharm, 25, 102–112 (2019). DOI: 10.18553/jmcp.2019.25.1.102*
14. *I Jacobs et al., Patient Preference and Adherence, 26, 937–948 (2016). DOI: 10.2147/PPA.S104891*
15. *European Commission, "Consensus information paper 2016. What you need to know about biosimilar medicinal products," (2016). Available at https://bit.ly/3fC6Zgk*
16. *FDA, "Biosimilars," (2021). Available at https://bit.ly/37nR5l1*
17. *EMA, " Questions and answers on biosimilar medicines (similar biological medicinal products)," (2021). Available at: https://bit.ly/3fyv5bG*

Think of the Patients

GlaxoSmithKline's Senior Vice President of US Oncology speaks with us about the pandemic and its impact on patients

The pandemic has affected numerous therapeutic areas by disrupting health services, leading to fewer patients being diagnosed, referred, and treated. In oncology, for example, many countries suspended public screening programs, which was consistent with the WHO's initial recommendations to minimize non-urgent facility-based care, and redeployed healthcare staff to assist with the pandemic. In cancer, early diagnosis and intervention is important to get the best outcomes for patients, and the pandemic is already having a negative impact on cancer patients.

Even before COVID-19, GSK's Senior Vice President of US Oncology, Mike Petroutsas, was concerned about how the industry interacted with patients. We speak with him about the importance of patient centricity and what patients want (and need) from pharma companies.

What are your views on patient centricity?

Patient centricity has been a buzzword both in and outside of the industry for a while. Of course, all of us in pharma want to get closer to patients, but in oncology, bringing that true human touch and approach is crucial. At GSK, we say that it's not about patients; patients are people first and foremost – so it's about people and individuals. There are so many barriers that pharma manufacturers need to break down when it comes to having these uncomfortable conversations about cancers, including racial, generational, and ethnic barriers. Until pharma is comfortable having these conversations, we can't become more patient centric. With cancers and other rare diseases, it's hard to apply a one-size-fits-all model.

You can speak with 10 different women who just went through chemo treatment for metastatic ovarian cancer, and are now contemplating the next stage of their disease and treatment, and they will all have a different treatment journey. Moreover, they will hail from different countries, some will have language barriers, and others may have generational challenges with children. Some of them may also encounter difficulties with accessing treatments. Each journey is unique and if you want to serve patients and truly break down the barriers they face, you have to see things through their eyes. I believe this is where pharma can have the most impact when it comes to supporting cancer patients.

"If you want to serve patients better and truly break down the barriers they face, you have to see things through their eyes."

What types of information do patients want from pharma companies?

I think this is one of the most misinterpreted areas in pharma. Market

research and information from advocacy boards has shown that the information patients are most likely to look for is on access to particular medicines. Often, however, pharmaceutical manufacturers predominantly focus on educating about disease, and providing supportive materials and information with regards to products and how to use them.

But if we take a step back, just getting access to medicines is key, whether it's through reimbursement, co-pay support, foundational support, Medicare, Medicaid, or even commercial programs. And this is really important during the pandemic when there is less accessibility to healthcare services. At GSK, we've pivoted from not only talking about education and our products, but to talking about access to medicines during the pandemic and showcasing the programs that are available to help patients. We need to make sure people can still access cancer treatments – and that they don't stop their treatment either.

How can pharma better engage with patients?

In the US, we are fortunate in that we have more opportunities to engage with patients compared with some countries. It's not just about direct-to-patient advertising – customized engagements through advocacy groups and advisory boards are also important, as is disease awareness and education. The early symptoms of ovarian cancer in older women, for example, can mimic menopause until certain things trigger the patient to take action and seek advice, so we need to be driving awareness.

And sometimes you need to be specific. When it comes to cancer, there is a tendency for companies to promote or discuss products in a general fashion to reach as many people as possible. In breast cancer, the overall survival rate has improved significantly over the last five years. But if you look at African-American women in the US – and specifically in states like Louisiana, where you have an underserved patient population from both an education and healthcare access point of view – survival rates have gotten worse. What are the reasons for this? It could be access to medicines, but we also need to understand some of the biases that exist around treatment, and the distrust that can exist around patient care. And that's what I mean by getting away from a one-size-fits-all approach. We need to customize patient education. The education doesn't always have to come through traditional forums,

Meet Mike

Mike Petroutsas is Senior Vice President of GlaxoSmithKline US Oncology

I'm originally from Greece and that is where I grew up. In a country like Greece, the healthcare system is complex and structured in such a way that the pharmacist is really your primary point of contact – and oftentimes your only contact until you get to a physician. I loved the service element of what they did – and the compassion and the way they empathized with and helped patients. I moved to the US in 1988 and I wanted to become a pharmacist. But I also loved science and I really got into infectious diseases. I actually ended up joining Pfizer and I worked on numerous programs. As my career progressed, I went from infectious diseases to rare diseases, and then ultimately into oncology. But, in my view, most cancers can be considered rare diseases.

As well as the science, I also loved the impact the work had on patients and their families. There's a big difference between rare diseases and more commonplace diseases in terms of how we treat and engage with patients. We have to be very particular with how we support our patients suffering from rare diseases. In many cases, there is a one-size-fits-all model in terms of how the pharma industry works with patients and this has to change.

This has been a driving force for me since I joined GSK. My mission, along with my colleagues, is to bring transformative medicines to patients. But we also have a lot of programs that focus on access to our medicines through patient engagement and social media, as well as education programs that provide support for patients and their caregivers (because in many diseases, particularly cancers, the caregiver is vital throughout the patient's journey). In drug development programs, there is a very controlled environment with specific support structures for patients. But it's a very different situation in real-world settings. You need to consider the fact that some patients can really struggle with how to access particular medicines, as well as the supportive care and education they need for their journey.

What makes me proud is when I have one-on-one engagements with patients and caregivers who tell us how GSK's medicines have changed their lives; it's probably the most fulfilling and energizing thing for our team. I also enjoy developing our associates. We've built a new oncology organization at GSK and brought in some really top talent. It's been a challenge – and a pleasure – to develop these people into even better, more patient-centric leaders.

like healthcare providers. In certain communities, pharma may need to reach out to local churches or affinity groups to understand how to build trust in the community. In short, we need to get a lot better at reaching different people – whether in different cities, states, or countries.

How has COVID-19 affected patients and the way pharma engages with patients?

COVID-19 has highlighted a number of discrepancies for underserved populations, including access to vaccines and to technology – and the worst outcomes for disease. At GSK, we noted a dramatic decline in wellness visits and I've been calling for people to go to these appointments. People need to take care of their health and get checked out if they are not feeling well. Surgeries in oncology have declined and diagnosis has significantly declined, which is concerning because it's really important to treat many cancers early. I think this is the first time in a very long time in our industry that we may see the five-year overall survival for many cancers actually get worse – and this will be because of delays in diagnosis. By the time people are diagnosed, they may already have progressed to a later stage of the disease, which will affect their outcomes. All of us in this industry must continue to educate and deliver the call to action to everyone we know.

We also need to consider the fact that COVID-19 has scared a lot of patients and has even brought out more mistrust. For example, there has been a great deal of misinformation about medicines for COVID-19 and vaccines. It will be important to build back trust in the healthcare system and in our medicines. Evolving R&D and clinical strategies is an important part of this. In particular, we need to bring greater diversity to our trials, which will help build trust in different communities. This isn't just about considering skin color and ethnic diversity in trial participants, but making sure the trial can accommodate different languages and accessibility needs.

At GSK, we think it is important to have diverse patient heroes and patient ambassadors that can encourage patients from different communities to take part in trials. With COVID-19, we've found that there's a lot of distrust of vaccinations amongst the African-American community because of the history that exists and previous trials that were misleading. We need to address these biases head on and make sure we are having the right conversations with different communities.

"Given that so many patients ask about costs and access, it means we're not doing a good job of explaining all the great programs that can help."

What else can the pharma industry do, in general, to address its bad reputation amongst the public?

In recent months, there has been a lot of positive attention on the industry because of the high-profile work of Pfizer, BioNTech, and Moderna on COVID-19 vaccines. And GSK is contributing to this too, through our collaboration with Sanofi.

There are many different elements associated with big pharma's bad reputation and this is something we get asked about a lot. One is the cost of care. We need to do a better job educating patients on the challenges that go into development and the high costs associated with this. There is also access. Given that so many patients ask about costs and access, it means we're not doing a good job explaining all the great programs that can help.

What developments in the oncology field are you most excited about for the future?

There are two areas. The first is mRNA. In oncology, we're used to chemo killing cancers, immune-oncology boosting response, and finding antibodies that target the right cancers. Gene therapy has shown us that we can manipulate genes and T cells to fight cancer, but with mRNA we can teach our body to fight a disease. mRNA has been used with some COVID-19 vaccines, but there's also work being done with HIV and MS – and in the future I hope we can use it in oncology too. COVID-19 has accelerated the move to mRNA therapies by giving us proof of concept.

The second thing I am excited about is the work we are doing at GSK around synthetic lethality and immuno-oncology – and some really interesting combinations. I'm really proud of the work my team has done. I've been at GSK for two and a half years, and since then we've launched four new indications fulfilling unmet needs in ovarian cancer, endometrial cancer, and multiple myeloma. When I joined, we had one oncology product in early development and today we have 14. We're all so proud as an organization to return to the oncology field.

Getting it Right from the Start: Simulation Optimizes Supply Chain Planning for Clinical Trials

Clinical supply chains are inherently dynamic and ambiguous, contributing to a high degree of uncertainty when trying to match drug supply to research needs at every stage of clinical development. By modelling this uncertainty, simulation tools can provide robust forecasts to help ensure investigational therapies get to patients when they are needed, and to reduce waste and development costs.

By Benedict Hirth

Managing clinical trial supply chains has always been challenging. Any delay or unexpected issue upstream in manufacturing or sourcing can impact available bulk quantities for every single downstream step – adding time and cost to clinical studies. The supply chain pressures exerted by the pandemic have exacerbated these challenges by an order of magnitude, as companies have had to adapt their supply strategies in real time when safety stocks run out, when plants shut down, or when shipments to clinical sites are blocked or delayed.

In the face of these uncertainties, early planning and demand forecasting using simulation tools helps companies to manage supply chain problems by setting the right priorities from the outset, anticipating the likelihood of disruption, and finding the best balance between risk and budget. A solid picture of demand supports management of expectations, steers communication with internal and external stakeholders, and assists with the setting of timelines and calculation of the right budget to feed the study. It also helps the bulk manufacturer plan for sufficient volumes and arrange appropriate timings for resupplies if batch sizes are too small.

Why simulate?

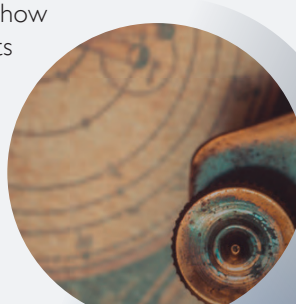
We all know that a rushed, unplanned supply chain will have consequences – the biggest being higher costs and higher risks. You may need to pack less material because of deadline pressure or because of supply shortages at the time of packaging. And that can lead to increased packaging activities, higher distribution efforts, and, ultimately, higher costs.

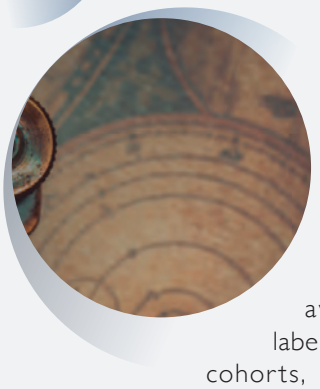
Further, many internal and external stakeholders are involved in the planning and execution of supply chains, meaning there are multiple interdependencies to manage and navigate. Having to do so in an environment of uncertainty and under extreme pressure increases the risk of error, which can negatively affect trial milestones and potentially compromise patient safety.

Deterministic tools – which can be as simple as an Excel spreadsheet – can assist with supply chain planning, but these tools can only calculate demand based on fixed parameters; they cannot show the potential impact of different patient enrolment scenarios, or of scenarios where different numbers of patients arrive for treatment each month, for example. When used at an early planning stage, a deterministic tool can also tie you down to a specific scenario based on early data – and early data are not always the most accurate representation of the future. In addition, deterministic tools tend not to consider shipment factors, such as shipment lead times and cost, Interactive Response Technology (IRT) settings, or the risk of late shipments, which can all have a significant impact on the clinical supply chain.

Ultimately, managing clinical supplies is a far more complex task than many realize. Patient enrolment and dropout are known to be highly dynamic, but there are also many other factors that can impact the supply chain. In my view, you can be better prepared if you consider your envisaged scenario and then investigate the effect of variability in different areas using simulation tools.

Simulation tools consider a large number of influencing factors on a supply chain model by executing hundreds of runs using different variables. For example, simulation can show what happens if all patients in the study attend in one month, and then zero patients the next month.





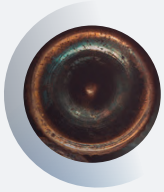
The runs can cover different country setups, enrolment plans, distribution setups, supply plans, expiry dates, available material, label groups, titrations, cohorts, packaging designs, bulk limitations, and more. What you're presented with is the likely outcomes – and the biggest risks. The simulation process can uncover potential issues that a standard human evaluation may miss, including their impact on the supply chain and likelihood of occurring. The data can produce suggested IRT settings, supply plans, shipment frequency, and quantities. Simulation also provides data to assist with depot shipment quantities and inventory management, and helps evaluate options based on risk and cost, while also considering any constraints, such as limited drug supply or limited storage capacity at sites.

The data output from simulation is only an assumption of what could happen. It's impossible to budget for every eventuality, but simulation allows you to see the biggest problems facing your trial, such as the risks of insufficient bulk quantities, unoptimized packaging designs, incorrect timelines, and so on. The data can then be used to inform supply strategy and to pivot resources to maintain the best balance between cost and risk.

Learning from the data

Recognizing the benefits, Thermo Fisher Scientific has invested in simulation and the expertise necessary to digest the data so that it can be read and understood by supply chain manufacturers without the need for modeling experience. We use Monte Carlo simulation, which brings variability within a defined framework into every single run. Monte Carlo is also considered a best practice approach for studying complex supply chains. There are many variables in how our clients set up their clinical trials it is important for us to use a tool that is flexible enough to work with different input data, including live data from the IRT, to re-evaluate supply strategies using real-time data.

Understanding the data output from the simulations requires fundamental knowledge of both clinical studies and the supply chain, including the distribution networks and IT systems, as well as a good understanding of the underlying statistical methods. Drawing the correct conclusion from the results is key to establishing a solid supply strategy. Our clients often want to investigate some very specific points or scenarios, so we work them to define the goals of the simulation and answer the questions they have about their supply chains. Because the quality of the models depend on the quality of the input data, a significant amount of data gathering is required at the outset. After the simulation, we create a report and discuss the results with the client and supply team to help them understand the simulation and how to adapt their supply chain as a result.



While deterministic tools are quicker to set up and more digestible for a supply chain manager, they do not offer line of sight into how variation or evolving reality may affect the supply chain, whereas simulation tools create models based on multiple scenarios to inform planning. Knowing the potential risks in advance is a key component of a strong supply chain. It allows companies to prepare alternative strategies to keep study timelines on track and maintain patient treatment if a serious issue should arise. Simulation is the most elegant and sophisticated way to gain such knowledge. Put simply, simulation is the next best thing to hindsight.

Benedict Hirth is Team Leader and Senior CSC Manager at Thermo Fisher Clinical Services

Top Benefits of Simulation

Cost versus risk analysis

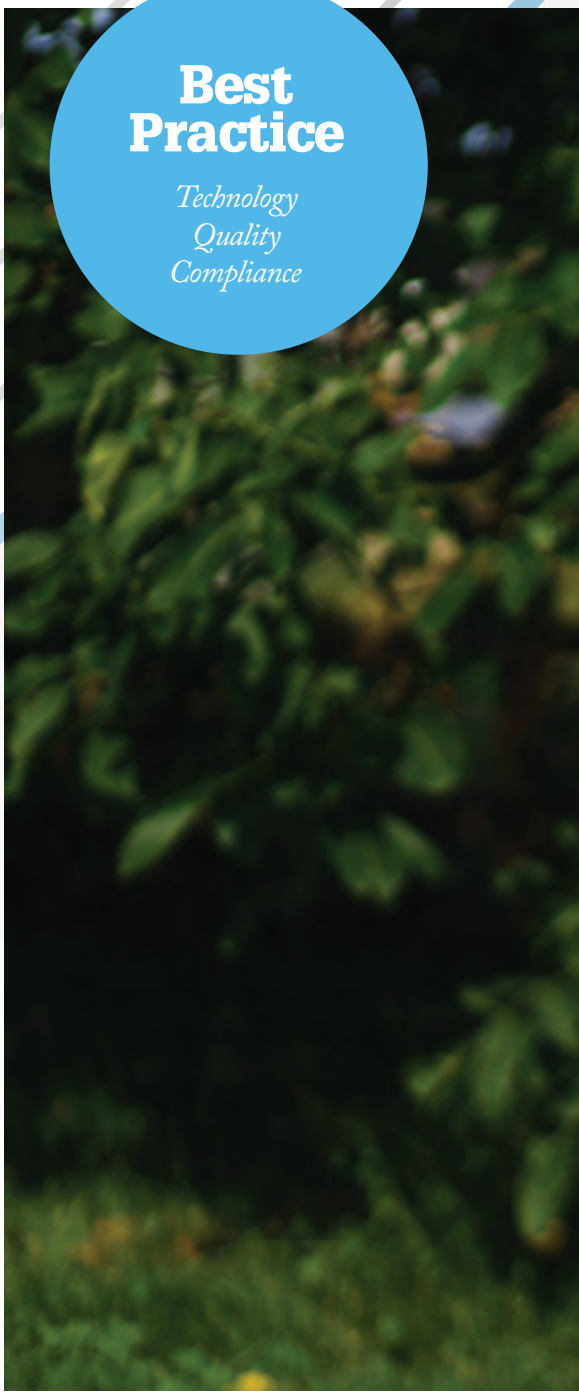
- Balance cost and supply chain risk/effort to execute the study

Material demand analysis

- Determine trial execution strategy if drug is limited
- Evaluate impact of expiry date on demand plan

Evaluate "What If" scenarios

- Evaluate different enrolment forecasts
- Evaluate different countries participating in the trial
- Evaluate different pack/label/distribution strategies



So, You Want to Become a CDMO...

Looking to pivot your business model to a CDMO service offering? Here's what to keep in mind.

By Sharon Johnson

The CDMO industry is fragmented with a vast number of companies occupying broad positions. CDMOs offer an array of services to help innovators accelerate products to market and assist in drug development – whether in the manufacture of drug substances or the formulation of drug products. In between these broad lines of division, there are numerous other disciplines, such as analysis, and other specialized services. Some companies market themselves purely on their niche capabilities, offering discrete and transactional services; others look to provide integrated services and collaborative development partnerships, effectively acting as extensions to the innovator's in-house team. No matter the nature of the company and the services it offers, the focus of a CDMO is to be customer-orientated and to deliver the best possible outcomes.

For an innovator company, the focus of R&D is science driven: discovering new chemical entities (NCEs) to target a disease and delivering treatment in the most efficacious way. Resources are centered on internal scientific excellence; business targets are set internally on project milestones and delivering the product portfolio.

The core competencies of a CDMO must be broader than that of an R&D company, whose value and unique selling points lie in invention and innovation. A CDMO must have the ability to take a molecule and, irrespective of disease target, develop and progress it towards becoming a treatment. The journey will be unique for each molecule, but the experience of other projects, and a wide range of cross-functional skills offered by a CDMO, are crucial for the successful development of a drug product.

Why become a CDMO?

The rewards and benefits of being a CDMO can be viewed in different ways. From a business point of view, the risk profile to the business is very different compared to an R&D company spending money on internal programs. For smaller companies, potentially with a limited number of promising candidates, the need for one of them to be successful determines the entire future of the company. And the number of successful projects in this industry, as we all know, is not as great as the number of projects that fail. By being a CDMO, the ability to work with a broad range of clients and having a diverse revenue stream reduces a company's financial exposure.

Additionally, there are personal benefits and rewards. For example, scientists working in a CDMO environment have the opportunity to broaden their experiences

by progressing a number of projects with various therapeutic indications. Science provides the opportunity to be creative, and working on diverse projects is a very different experience and role than working on a single project for a prolonged period of time. A CDMO's strength is in the motivation and knowledge of its scientists; and the greater exposure they get in solving challenges and overcoming problems, the more experience they gain for future projects.

The satisfaction that can be achieved as a company that is part of a successful drug launch is also a factor that cannot be overlooked or overemphasized. As a CDMO, working on projects at various stages throughout their development, and to enable a molecule to become a treatment, is highly motivational for all staff. Success breeds success, and so, as the number of products launched increases that have been worked on by a CDMO, there is a sense of pride that comes with having a positive impact on a broader patient population. This not only enhances the reputation of a CDMO but

increases its appeal to innovators.

But how do you, as an innovator company, change your business strategy to become a CDMO? And what are the differences that you must make during the transition? What should your main priorities be and how will you measure success?

The most important consideration is understanding what needs to stay the same. The same excellence in science and focus towards what is important does not change, and there will always be a patient at the end of every project. There will be a customer contract in place – but the final customer and ultimate goal will always be to meet patients' needs.

It is vital that you keep scientific excellence at the core of your business: talent, expertise and experience is what attracts customers to working with partners. In my experience, this the most important selling point for any CDMO: mediocre services do not cut it.

From that core, the individual layers of service, procedures and values can be built up to create an offering. Some will be similar to undertaking internal R&D, but others are very different. You need to weave all of these layers together to create a positive "customer experience" that allows you to differentiate your company within the market.

Deciding on your structure

A good first step is to define the CDMO process and the company structure; roles and responsibilities should be well defined, so it is clear who is accountable for each step. The expectations of "what good looks like" need to be clarified, and a feedback mechanism should be established to assess progress in a transparent and honest way – in fact, this is crucial given the importance of customer service in a CDMO business model.

Put simply, the CDMO end-to-end process can be split into six distinct phases: i) customer engagement (pre-quote), ii) quoting, iii) ready to execute, iv) project execution, v) project close out, and vi) customer feedback. By going through this cycle multiple times with a continuous improvement mind-set – and based on a foundation of quality and regulatory compliance – you'll soon have the foundations for your service provision. A CDMO also obviously needs a business development team to engage with potential customers, but operationally, the company needs to be in a position to be marketed effectively; you need the capability to handle multiple (and likely diverse) projects simultaneously – each to the highest standards. In other words, your internal processes need to be fit for purpose so that you can please your customers.

To ensure quality and delivery, you'll need to establish a way of working that is standardized but agile enough to respond to challenges. In the CDMO world, no two projects are identical. The overall product development approach and processes are well-established in our industry, and governed by long-established regulatory requirements for quality, safety and efficacy of the product. And that does not change in the CDMO environment. What's different? The nuances of interpretation of customer requirements. Each customer may also have their own best practices that can potentially increase complexity. As a CDMO develops and matures, you'll need to have a continued focus on simplification, balancing standard ways of working with adapting to any bespoke needs of a project. You must be able to provide timely and transparent feedback to customers that can let them make the right go/no-go decisions.

Adapting to the customer

My experience in working within the CDMO space has taught me that it is important to act as an extension of

"The strength of scientific talent lies in the ability to extrapolate experience and expertise to something new."

your customers; that's how customers should feel when working with a service company. And though it may sound obvious, for a company changing from a research-led ethos to an external service provider, it can be challenging to adjust to the customer service mindset! Communication – the basis of your relationship with customers – will be one of your most important skills. You must ensure there is unambiguous alignment about the scope of work being requested, you need to be proactive in providing solutions to development challenges (which there will be – I assure you of that!), and you'll have to be responsive, flexible, and available – all while safeguarding the foundation of the company as a contract provider so that the business continues to be stable in the future.

Clear communication brings trust and openness. As a CDMO working on different projects – and in some cases on projects in closely-aligned areas – a clear policy on confidentiality will be paramount; it should be mandated in all employee training and education, and reinforced through everyday working practices.

There will be challenging situations. And, at times, there may be difficult conversations to be had with your customer about a project. Again, you must be clear and honest in these discussions. And then you need to mobilize resources rapidly to minimize any disruption to your customer's project plan. You will probably need to think outside of the box and believe a solution is possible.

In a CDMO organization, everyone is a salesperson irrespective of their role; for every customer, every moment and every touch point matters – with whomever they interact. I've seen many occasions where a project's success is defined by technical teams from both sides share insights and solutions that are credible and achievable, demonstrating the CDMO's expertise.

For innovators transitioning into CDMOs, enabling regulatory success of projects may be one of the more familiar areas in which to provide assistance to customers. As an innovator, you'll already have experience in developing products and navigating the regulatory landscape; as a CDMO, you'll have the opportunity to anticipate, determine, and recommend strategies to customers less-versed in the journey, which is very rewarding. Every customer will have differing levels of need, but having the depth of expertise to challenge as appropriate and to suggest alternate paths is important.

Staying ahead

When choosing CDMOs, companies often look for investment in terms of both innovative technologies and scientific talent. Innovators want to see CDMOs looking forward, anticipating the next trends in their area of specialism. Looking at new equipment and technologies is the easier of the two; you just buy what you need. Your in-house experts, however, will be absolutely core to your business. Indeed, knowledge and scientific talent is the true capital investment, so knowledge retention and creating an environment for career growth in a changing paradigm will be key to the success of your business.

The strength of scientific talent lies in the ability to extrapolate experience and expertise to something new – to harness scientific curiosity for creative problem solving. And it creates huge amounts of value for a CDMO. After all, CDMO scientists are exposed to a much more diverse range of molecules, indications, and technology, which feeds their imagination – but they are also driven by the need to find solutions within a target timeline to deliver the target product profile. Being on someone else's clock creates a different perspective and urgency at times, and for some scientists this is a big step (and change!). Appropriate management and support is vital to ensure the transition can be made successfully – you don't want to lose talent…

While making the transformation, continue to review your processes and practices, and evolve to the current market demands. (Sidenote: Changing your business model a few months before the start of a global pandemic is not ideal – try to avoid that if you can!). A CDMO always needs an answer to "What do we do about this – and how do we get to yes?" The importance of this cannot be understated. Today, the need to adapt and adjust has become both a necessity and a strength during these extraordinary times.

Leadership drives the company. And for success to lead to growth and longevity, you'll need transparent, actionable key performance indicators to ensure accountability with a continuous improvement mindset.

In the highly competitive CDMO industry, I have long held the belief that only excellence is tolerated.

Sharon Johnson is Executive Vice President for Delivery Management at Vectura

Leadership Star

Sitting Down With… Andrew Moore,
General Manager of Pfizer CentreOne,
Pittsburgh, Pennsylvania, USA

Did you always want to be a leader?

I thought I wanted to be a lawyer, but I couldn't afford law school. I decided to join the military because my family has a long history of military service. After that, all I knew was that I wanted to be a leader in something… I've always enjoyed leadership roles; at college, I was captain of the university track and field team.

The military is the foundation of my leadership skills. To me, the definition of pure leadership is the ability to get things done through others. This is what the military teaches young officers. When you join, you don't know very much. You have to listen to your sergeants and learn from them, so that you are prepared when the time comes for you to lead in the field.

How did you get into pharma?

I like to tell this story! In the army, my specialty was nuclear, chemical, and biological warfare, so people associate that with a link to pharma. But the truth is that I fell into the industry in a very different way. One of my soldiers married the daughter of the international president for Baxter. I attended the wedding and the father of the bride and I got along well. In fact, he convinced me to consider working for pharma... and then he actually offered me my first job in the industry! I did some research and realized that it was interesting and could really help people – which was important to me. Pharma also seemed to be at the cutting edge of technology. I wanted to be part of it.

What was your first role?

It was in sales. I did my whole year's budget in the first nine months and was promoted to product manager. From there, I moved up the rungs of the marketing ladder. I eventually left to work for Becton Dickinson, where I ran North American operations for the hypodermic business. I spent seven years at Pfizer before leading the Northeast region of pharmaceutical distribution and business operations at McKesson. In time, I became CEO of CogxVision and then, in 2020, I joined Pfizer CentreOne. Pfizer is where I experienced the most personal growth in business. It was nice to come home.

What was it like to start a new role during the pandemic?

I was interviewed via WebEx, joined the team the same way, and still have not met many of my colleagues face-to-face. It is a challenge, but this new environment has also, in some ways, made us more productive. WebEx meetings can help get things done in terms of driving decisions. Previously, you'd be trying to get people from all over the world to come together at one location for a meeting. There is nothing better than face-to-face contact, but there can also be a lot of wasted time. Without COVID-19, I would still be travelling around the world meeting team members globally. Instead, it is all done via WebEx. I've missed out on the opportunity to bond outside of work, but I've met more people across the organization than I would have if I'd been in the office every day.

What are your goals for the business?

We aspire to be the CDMO partner of choice. We have been expanding our offerings so that we are truly an end-to-end CDMO, from development through to commercial manufacture. We are fortunate to have access to Pfizer's resources and expertise. This is our value proposition.

How do you motivate teams?

I believe it is important not to see failure as a negative. One company I worked for was very operationally driven, rather than being driven by sales and marketing. There was very little coming out of the sales and marketing teams in terms of figuring out ways to be creative in the selling process. I challenged the team and they came up with three or four different projects to help boost sales. We all agreed on one and launched it. It failed within the first 30 days. But I took the team curling to celebrate. They had a great day. Why did we celebrate? Because we did something different. After that, the team came up with several new opportunities. We launched them and, in 12 months, we took the business from a 2 percent decline to 12 percent sales growth. I believe you should celebrate not just success, but also honest attempts at doing something different. There is much to learn from failure.

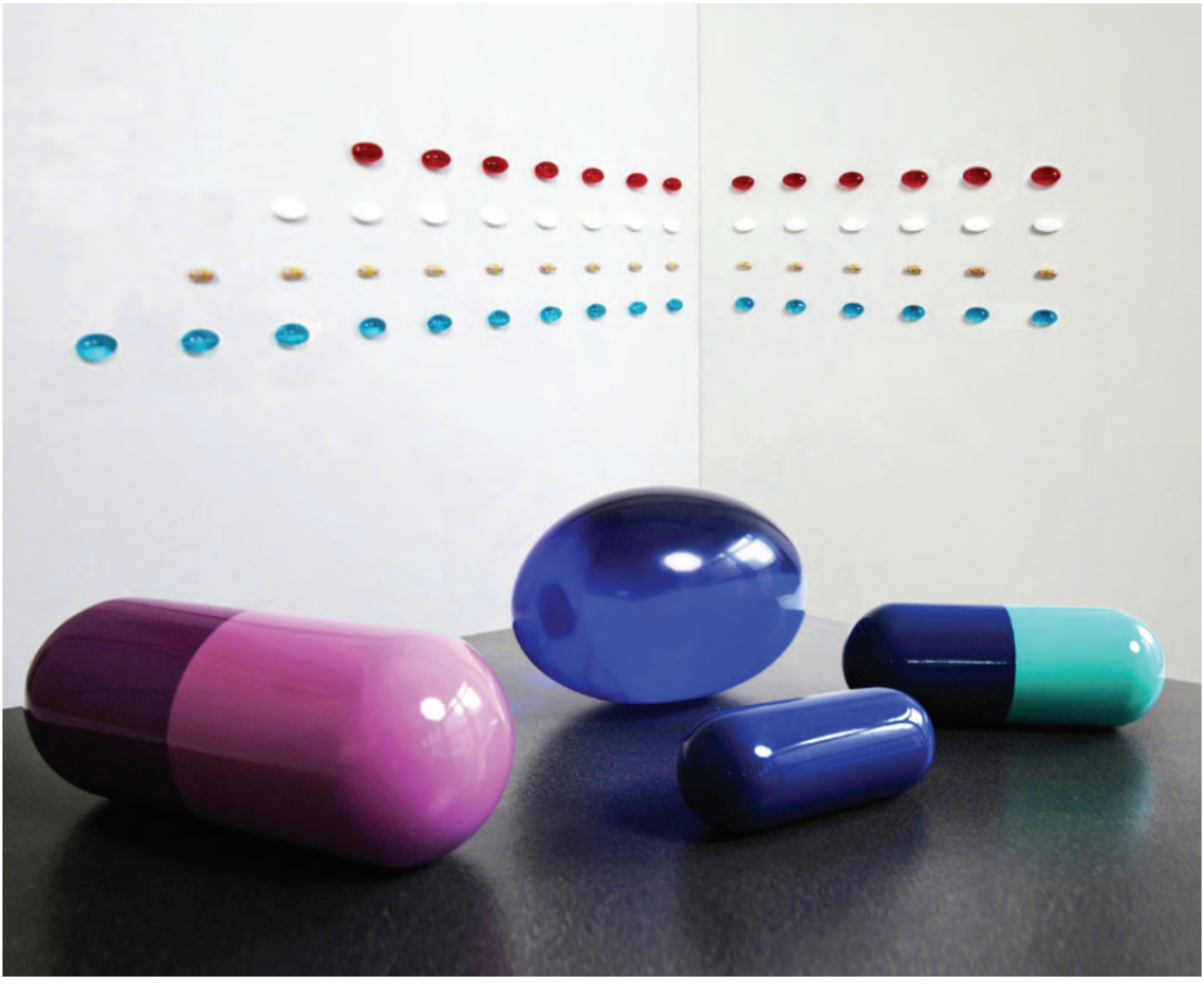
"Listen at least three times more than you speak. Listen and learn."

What's your advice for people who want to become leaders?

Listen at least three times more than you speak. Listen and learn – this is particularly important for younger people just starting out in the industry. But don't hold back on ideas. There are no bad ideas.

You may also need to ask a lot of questions – particularly if you don't have a strict scientific background. It's always better to ask. I don't think anyone expects us to know everything, but you shouldn't continue on with something you don't understand. And I can guarantee that there will be someone at every meeting who will be really glad you asked the question.

One thing you will find in this business is that everyone is willing to help. That's what I really love about this industry and about Pfizer. Everyone wants to succeed but everyone really wants you to succeed too.



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