MAY 2018 # 41

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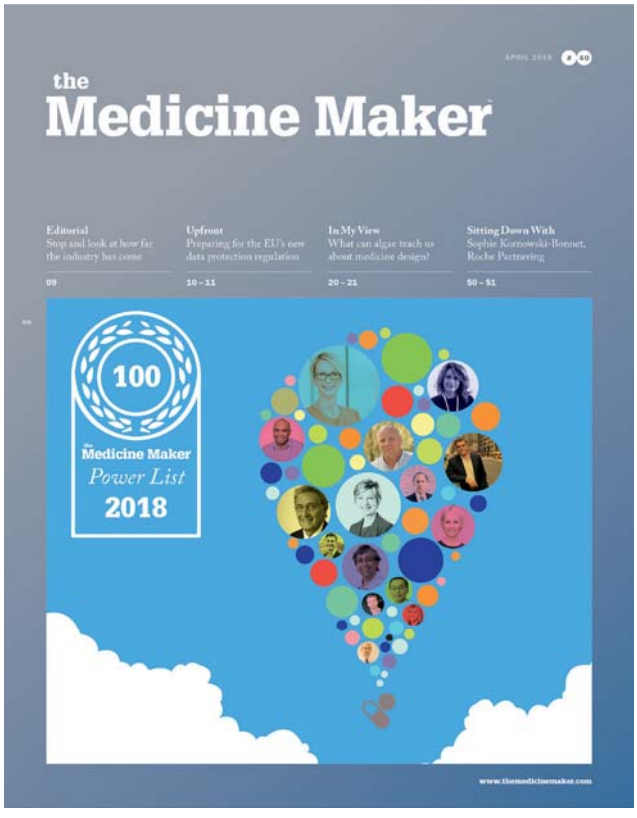

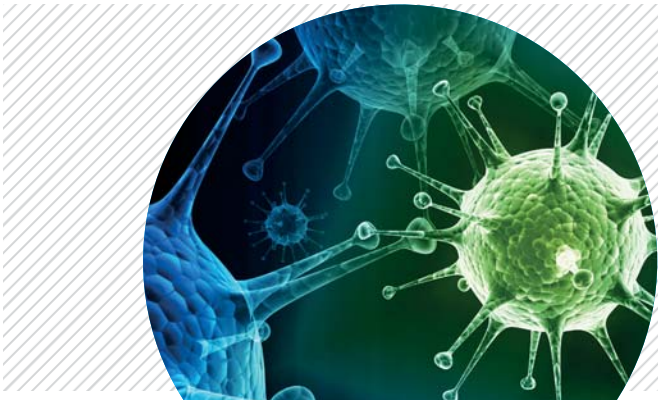

The Power List 2018

Did you miss out on the April 2018 print issue of The Medicine Maker? Our April issue included our annual Power List of the top one hundred professionals in drug development divided into four categories: Masters of the Bench, Industry Influencers, Business Captains, and Champions of Change.

Want to find out who topped each category? You can view the full list on our website: https://themedicinemaker.com/power-list/2018/

Or check out our social media coverage of the Power List:

Twitter @medicinemaker
LinkedIn Showcase The Medicine Maker
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And Coming Up Next Month….

The three top winners of The Medicine Maker 2017 Innovation Awards – SGS, OUAT! and GE Healthcare – share the stories behind their technologies. And look forward to the opening of nominations for the 2018 Innovation Awards!

Contents

On The Cover

Biosimilars seek to change the world through love, lower drug costs and improved access for all.

Upfront

the Medicine Maker

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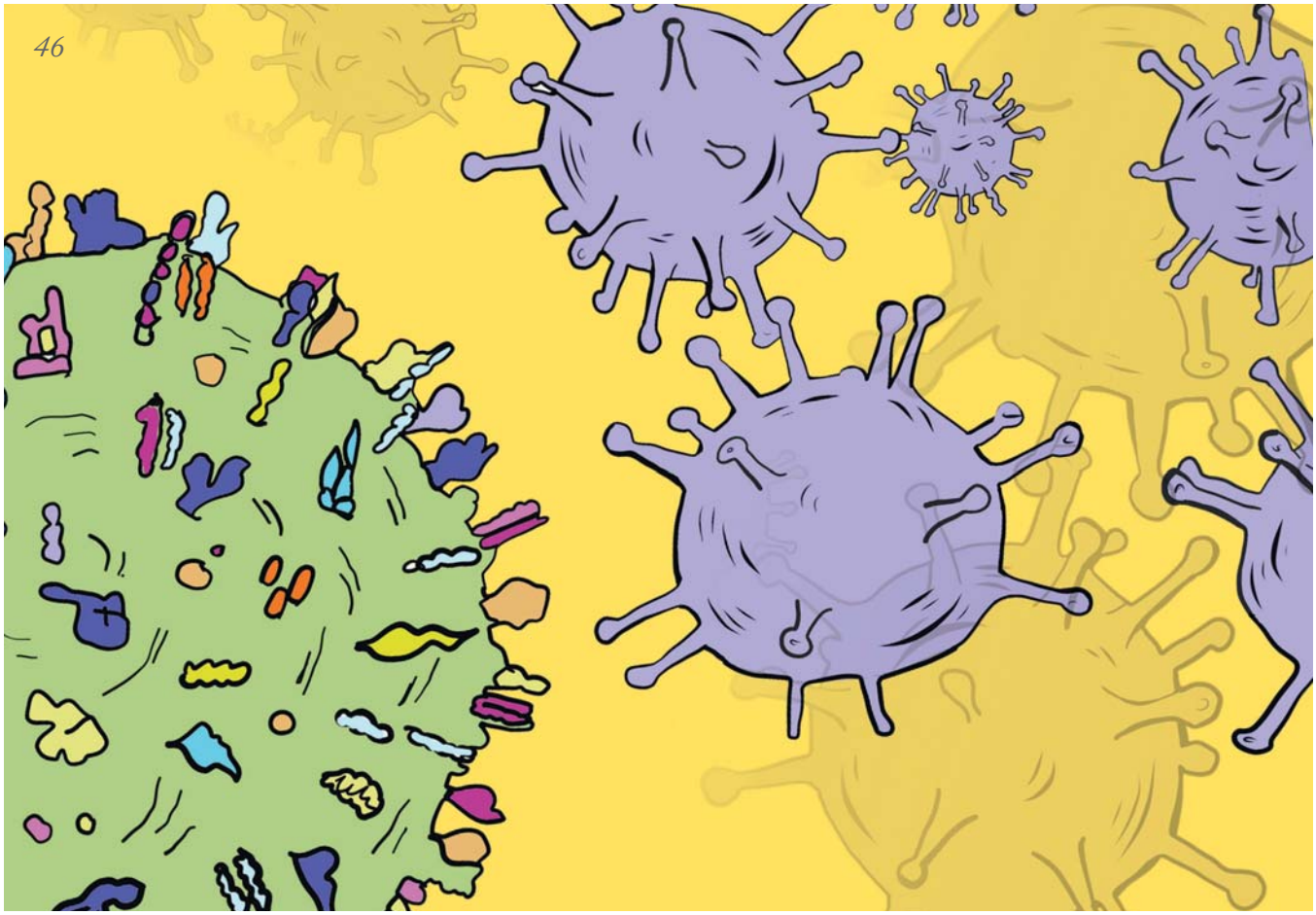


In My View

Feature

Reports

NextGen

Sitting Down With

Open Your Mind

Is the pharmaceutical industry overly reluctant to accept new ideas?

It is universally acknowledged that the pharmaceutical industry can be conservative and slow to embrace change. With the health and safety of patients at stake if something should go wrong, this is hardly surprising. But does pharma's skepticism run too deep?

I recently had the pleasure of speaking with Alex Zhavoronkov, CEO of Insilico Medicine – a passionate supporter of artificial intelligence (read more on page 40) and a true believer of its transformative potential in drug discovery. Insilico Medicine is working with Juvenescence to identify preclinical compounds, but there are other companies grabbing headlines in the AI/pharma space; take BenevolentAI, which is attempting to gain new insight into the molecular mechanisms of disease and to match patients to the right drug. The company was valued at $2 billion after its latest round of funding (1).

AI has been touted as a technology to watch for some time across diverse industries, so I was a little surprised when Alex told me about the skepticism and disinterest he'd encountered within big pharma.

"AI is moving too fast."

"AI isn't ready for primetime."

AI is certainly new ground for pharma, so perhaps (healthy) skepticism is to be expected. But what about more established industry innovations, such as biosimilars? Biosimilars have been available in Europe for years but skepticism remains. In our cover feature on page 26, several experts tackle common safety "myths" and lay out the path towards more rapid adoption – in a word: education.

Both AI approaches and biosimilars have the potential to transform our industry. So it seems a shame that proponents must waste time and energy on the seemingly Sisyphean task of "arguing the case" rather than developing innovative lines of thinking. Though there will always be those who are ahead of the curve in science, perhaps pharma as a whole could benefit from keeping a more open mind – providing patient safety comes first, of course.

Roisin McGuigan
Deputy Editor

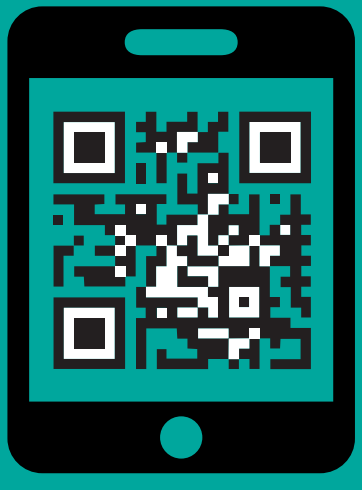
References

1. *CNBC, "AI pharma start-up BenevolentAI now worth $2 billion after $115 million funding boost", (2018). Available at: bit.ly/BenevAI. Accessed May 4, 2018.*

Upfront

Reporting on research, personalities, policies and partnerships that are shaping pharmaceutical development and manufacture.

We welcome information on any developments in the industry that have really caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com



Print it, Eat it

Could drug-containing QR codes fight fakes and avoid medication errors?

With the rise of the smartphone, we have all become familiar with the QR code – used for everything from boarding an aircraft to paying for a service. But what if you could eat one and receive a dose of medicine?

A team from the University of Copenhagen have taken the QR code a step further, creating a system to print QR codes on to an edible material as a means to create personalized medicines. "It actually started out as a funny idea briefly discussed over lunch," says Natalja Genina, co-author of the associated paper (1) and assistant professor in the Group of Manufacturing and Materials at the University of Copenhagen. "Then we realized that it could actually be used. First, we identified the gaps in conventional medicines. Second, we pinpointed the unique possibilities of inkjet printing technology that can be used in the production of medicine. And, as the world is now driven by digital devices and interconnected through the Internet of Things, we used our creativity and knowledge to combine all the factors and came up with the idea of the edible QR code".

The team uses ink-containing active pharmaceutical ingredients, which are placed on an edible "paper" in the form of a QR code using inkjet printing. The QR code is resized to produce the right dose, and contains a host of relevant information – which can include the patient name, the dose, manufacturing information and expiration dates, and more. "On average, it takes around 4 to 7 minutes to print therapeutically relevant doses with the advanced printer we used in this study," adds Magnus Edinger, a PhD fellow who worked on the project.

Genina says the system has the potential to tackle counterfeit medicines and medication errors. "Current medicines are mostly in the form of plain white tablets with few, if any, distinguishing characteristics. This can potentially allow counterfeits to enter the supply chain. Incorporation of QR codes as anti-counterfeiting features can help minimize the risk of getting a fake medicine. The encoded information will also ensure that the patient takes the right medication at the right time and in the right way. For example, an alarm can be encoded into a mobile phone, reminding the patient to scan and administer the QR code dose," explains Genina.

Genina and her team believe the technology is ready for implementation, but it will be difficult to predict when it may hit the market. She adds, "We are now studying the following scenarios: manufacturing of patient-oriented medicine at the pharmacy, in the pharmaceutical industry, and even in the patients' home."

Reference

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Wake Up and Smell the Polymer

Caffeine isn't just a catalyst to get you moving in the morning – it can also help create polymers for drug delivery

Biocompatible gels have a range of applications in the pharma industry, including drug delivery. Giovanni Traverso, assistant Professor of Medicine at Harvard Medical School and a gastroenterologist in the division of gastroenterology at Brigham and Women's Hospital, along with his collaborators at the Massachusetts Institute of Technology, is working to develop new polymer gels with improved safety profiles. The majority of gels are created using traditional metal catalysts, which can pose a toxicity risk if any of the catalyst remains in the gel after it is formed.

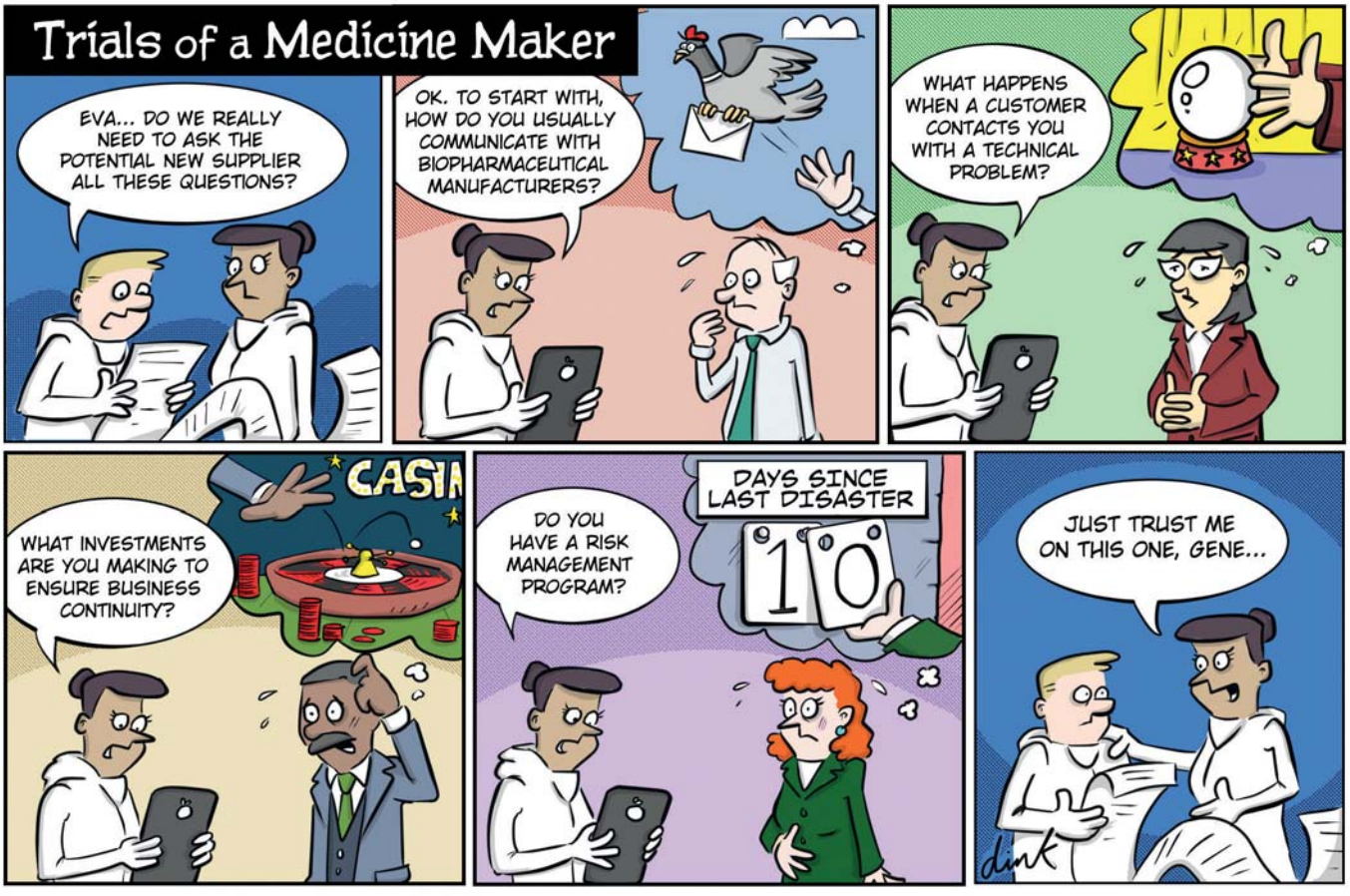
In particular, Traverso and his team have hit upon a novel catalyst with low toxicity in the form of the well-loved friend of the coffee drinker: caffeine (1). "We used caffeine, a weak base, to catalyze anhydrous carboxylate ring-opening of diglycidyl-ether functionalized monomers with citric acid," explains Traverso.

The gummy polymer gels created using this method could have a range of applications, particularly for patient populations who have difficulty swallowing capsules and tablets. It's also possible to fine-tune the properties of the gels. "We have demonstrated the capacity to tune the surface properties of these gels by recreating the surface pattern of the lotus leaf on the gels and thereby modulating the hydrophobicity of the material," says Traverso. Altering the gels in this way could be used to impact how quickly or slowly they move through the patient's digestive tract.

Reference

1. *AM DiCiccio et al., "Caffeine-catalyzed gels", Biomaterials, 170, 127–135 (2018). PMID: 29660635.*

For more adventures featuring Gene and Eva check out our website themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



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Kjetil Ree

Go Forth and Find a Flu Vaccine

Bill Gates has issued a challenge – and significant funding – to help researchers push for a universal flu vaccine

The year 2018 marks the centenary of a flu pandemic that killed around 50 million people worldwide. Since then, significant efforts have been made to fight the flu, but a universal flu vaccine still eludes us – and thousands continue to die every year. In late April, the Bill and Melinda Gates Foundation launched a $12 million Grand Challenge: "[to] identify novel, transformative concepts that will lead to development of universal influenza vaccines offering protection from morbidity and mortality caused by all subtypes of circulating and emerging (drifted and shifted) Influenza A subtype viruses and Influenza B lineage viruses for at least three to five years".

The foundation is looking for "bold ideas" and "unconventional approaches" – not marginal improvements or precedential approaches, such as the use of biosimilars, monoclonal antibodies, or the development of new assays, adjuvants, and so on. Examples of what the foundation is looking for include:

- Antigen-centric: discovering new antigens/targets through artificial intelligence or deep learning.
- Host-centric: approaches that generate, enhance, or modify human immune protection, or that ensure longer term immune response.
- Technology-centric: including novel vaccine concepts, targets and constructs inspired by new understanding about the nature of the influenza or immune response; and applications of new technologies for disease protection.
- Enabling advances: including challenge models to quickly demonstrate safety and proof-of-concept for influenza vaccines.

The aim is to develop a vaccine that is ready to start clinical trials by 2021. Pilot funding will be offered in the region of $250,000 to $2 million. Upon the demonstration of proof-of-concept, projects will be invited to apply for a full award of up to $10 million. Applicants don't need to have an industry partner, but such collaborations will be considered. Industry is also welcome to apply.

If you think you're up to the challenge, bear in mind that the deadline for submissions is June 22, 2018: https://bit.ly/2HwEI7F.

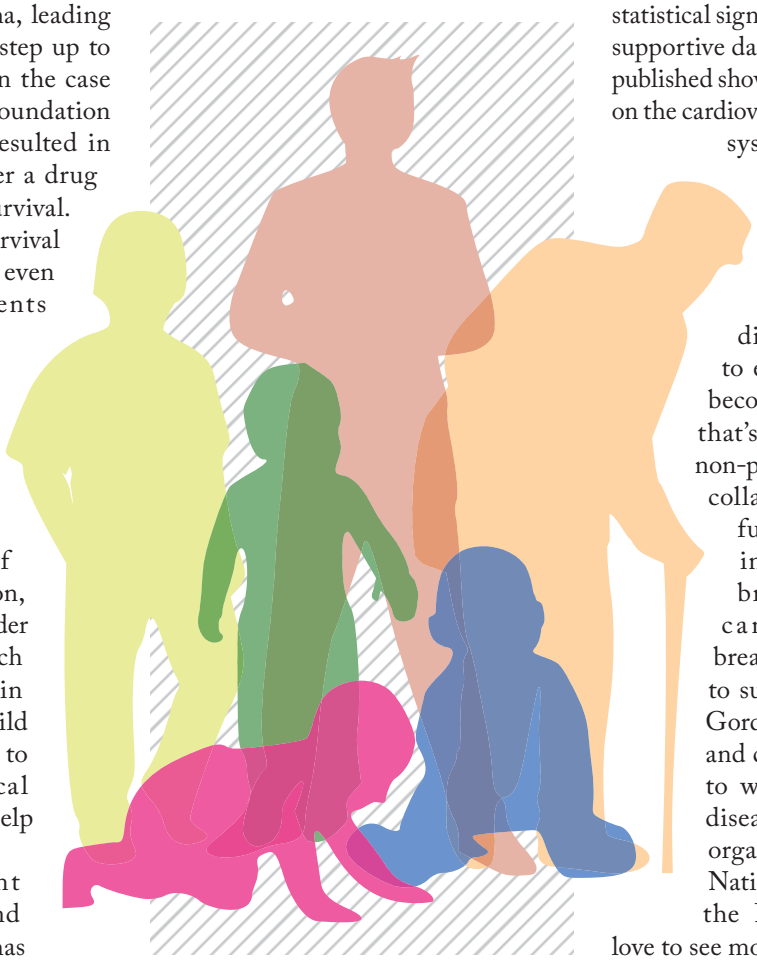
A Life Too Short

Researchers celebrate a new breakthrough into progeria, and urge others to help them find a cure

Countless rare diseases remain uninvestigated by big pharma, leading non-profit organizations to step up to the challenge themselves. In the case of the Progeria Research Foundation (PRF), their efforts have resulted in gold – for the first time ever a drug has been shown to increase survival. Clinical trials that increase survival are always heartening, but even more so when the patients are children.

"Progeria is a rare, fatal, pediatric disease that causes rapid aging. Without progeria-specific treatment, children with progeria will die of heart disease at an average age of 14 years," says Leslie Gordon, medical director and co-founder of PRF. "The Progeria Research Foundation was founded in 1999 by the parents of a child with progeria, in response to a complete lack of medical and scientific progress to help these children."

Working with patient families, pediatricians, and academic researchers, PRF has uncovered a number of scientific insights into progeria.over the last two decades. The disease is caused by a genetic mutation in the LMNA (lamin A) gene, and results in the over-production of a protein called progerin, which causes premature aging of the body's cells. After the gene discovery, PRF-funded researchers began an intense study of progerin and its post-translational processing. "There is a real biological link between progeria and normal aging. We now know that progerin is made in all of us, but at a much lower rate than in children with progeria. Progerin is found in cells of the cardiovascular system and increases at about 3 percent each year that we age," says Gordon.



The discovery led researchers to investigate Farnesyltransferase inhibitors (FTIs), particularly FTI lonafarnib, which has mainly been studied in solid tumors. To block normal cell function and cause progeria, a farnesyl group attaches to the progerin protein. Since FTIs inhibit attachment of the farnesyl group, it was theorized that they could help progeria patients.

Treatment with lonafarnib alone compared with no treatment was associated with a significantly lower mortality rate (3.7 percent versus 33.3 percent) after a median of 2.2 years of follow up (1). "This is an incredibly short amount of time to achieve statistical significance. And we also have supportive data that we have previously published showing lonafarnib's influence on the cardiovascular system and skeletal systems. It shows us that we can make progress," says Gordon.

But she also stresses that pharma needs to do more to support rare diseases. PRF is hoping to eventually see lonafarnib become FDA approved – but that's a huge challenge for a non-profit organization and its collaborators. "We need to fund much more research into progeria. There are brilliant scientists that can help us make big breakthroughs, but we need to support their efforts," says Gordon. "The only way to treat and cure these fatal diseases is to work together – the rare disease communities, patient organizations, academia, the National Institutes of Health, the FDA and pharma. I've love to see more incentives and rewards for pharma to get involved with rare diseases. This is an opportunity to save children – and make new discoveries in aging and atherosclerosis."

Reference

1. *LB Gordon et al., "Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome", JAMA (2018).*

Staying on Target

What characteristics make a cancer therapy more likely to effectively treat disease?

Targeted therapies have had a huge impact on cancer treatment, in some cases significantly improving patient survival – but not in all cases. To treat the cancer, the drug must, of course, reach the tumor tissue and be taken up by cells, but this doesn't always happen effectively despite targeting efforts. Why not?

Tumors and their surrounding environments are complex and heterogeneous – resulting in different responses to the same drug. Katarzyna A. Rejniak and Aleksandra Karolak of the Rejniak Lab at the Integrated Mathematical Oncology Department at the H. Lee Moffitt Cancer Center & Research Institute in Tampa, Florida, are part of a team that has combined mathematical modeling and single-cell imaging of cancer cells to better understand what drug properties make for more efficient drug uptake (1). Here, we find out more.

What inspired you to investigate this problem?

Katarzyna A. Rejniak (KAR): Our extended team combines mathematicians, chemists, biologists and image analysis experts. Working in the Cancer Research Institute allowed us to participate in seminars in which pathologists and cancer biologists discussed the use of medical images in cancer diagnosis and treatment monitoring. We decided to use tumor tissue histology images or fluorescent images as a domain for mathematical models and to test whether drugs or imaging agents will penetrate tumor tissue differently depending on cellular and stromal architecture.

How does your approach work?

KAR: The Analytic Microscopy Core at our Cancer Center provide us with digital images of tumor histology. We then develop computational routines to discretize these images, select tumor cells, determine their sizes and shapes, and use them in our computational models. Our models also contain drug molecules with pharmacokinetic and pharmacodynamic properties of experimental drugs or biomarkers. We run multiple simulations in which we change some drug properties or drug administration schedules to see if we can achieve more efficient drug

distribution within the tumor tissue and individual cells.

What drug characteristics did you find to be most important for uptake?

Aleksandra Karolak: The answer is complex… The successful recognition of drug molecules by receptors and high affinity binding plays a pivotal role in the formation of drug-receptor complexes. However, we didn't quite expect to see that the fast release scheme of a drug could lead to increased uptake for moderate affinity drugs. On the other hand, because of multifaceted barriers, efficient drug uptake by cells with limited access to drug molecules won't be improved until receptor-ligand contact takes place. Here, the impact of affinity and release scheme becomes less important, at least until drug molecules reach the distant cells. For this to happen, some biophysical and biochemical drug properties including size, molecular weight, charge, hydrophobicity, or conformation must be adjusted. In our model, we vary these drug properties to explain on the single cell level why certain drugs could be more successful in reaching distant cells than others.

What's next?

KAR: We hope that micro-pharmacology techniques developed by us and others will allow drug efficacy to be tested within the tumor tissue before the drugs are tested in animals. We are starting to examine how to stratify tumors to match them with the most effective treatment based on our simulation studies. The current plan is for animal studies first, but we hope that this approach will have translational potential. One of the outcomes of our published work was that by changing the way the same drug was administered (slow or fast release) it was possible to either saturate cells located near the vasculature or far from the vasculature. Thus, we proposed a way to predict how to administer a drug to increase its effectiveness.

Reference

1. *A Karolak et al., "Targeting ligand specificity linked to tumor tissue topological heterogeneity via single-cell micro-pharmacological modeling", Sci Rep, 8, 3638 (2018). PMID: 29483578.*

Business in Brief

A knockback for biosimilars in the US, patient engagement, and contaminated blood products... What's new for pharma in business?

Facilities

- The UK's Cell and Gene Therapy Catapult has opened a manufacturing center in Stevenage, UK. The center was backed by over £60 million from the UK government and has the infrastructure to develop manufacturing capability for large scale cell and gene therapy clinical studies. The center will also supply the network of world-first, UK-based Advanced Therapies Treatment Centers, which will develop and deliver the therapies.
- A new R&D center is on the cards for WuXi AppTec, which has just signed an investment agreement with the government of Shanghai Jinshan District in China. The new center will be located next to the existing Jinshan drug substance manufacturing site, and will add more than 30,000 square meters of laboratory space and 500 scientists.
- In the US, Mayne Pharma has opened a new $80-million facility, which will quadruple the company's capacity to manufacture oral solid-dose pharmaceuticals. The facility is located in Greenville, North Carolina, and can also cope with the commercial scale manufacture of potent compounds.

Biosimilars

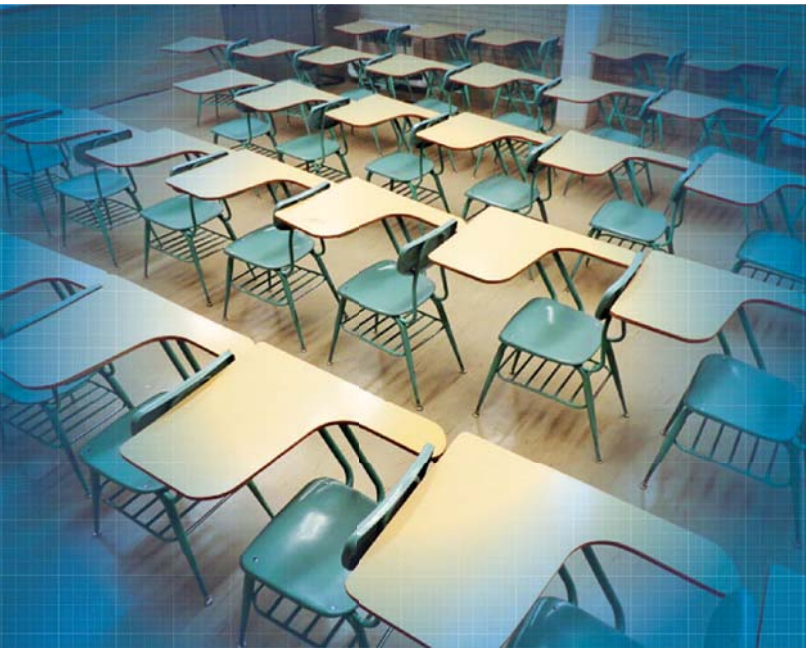
- Sandoz's rituximab biosimilar application to the FDA has been rejected. The company received a complete response letter in early May. The reasons for the rejection have not been disclosed. "While disappointed, Sandoz remains committed to further discussions with FDA in order to bring this important medicine to US patients as soon as possible," Sandoz said in a statement. Rituximab was approved by the EMA in June 2017 and is marketed as Rixathon.
- Herzuma, a biosimilar trastuzumab (Herceptin), is now available in Europe for the treatment of early breast cancer. It is the third biosimilar to be marketed and distributed by the Mundipharma network in Europe. Marketing authorization was granted in February 2018.
- A report from ResearchAndMarkets.com (Biosimilars Market by Product, Manufacturing Type and by Disease – Global Forecast to 2023) has forecast the global market for biosimilars to grow at a CAGR of 31.7 percent, to reach $23.63 billion by 2023. The non-glycosylated proteins segment accounted for the largest market share of the market in 2017; however, recombinant glycosylated proteins are expected to hold the largest share of the market during the forecast period.

Collaboration

- PARADIGM is a new collaboration between 34 public and private partners, launched to make "meaningful patient engagement in the life cycle of medicines a reality". PARADIGM stands for Patients Active in Research and Dialogues for an Improved Generation of Medicines, and is funded by the EU's Innovative Medicines Initiative. It is described as an open forum on patient engagement.
- AstraZeneca is collaborating with Lucy Cavendish College at Cambridge University to help women advance in science and business leadership. Employees will mentor students by supporting their scientific developments and offering career and personal development advice.

Controversy

- A public inquiry will begin in the UK later this year on the tainted blood scandal of the 1970s and 1980s, when more than 3000 people were infected with HIV and Hepatitis C. Campaigners are pushing for the inquiry to examine the role of pharmaceutical companies.
- Biohacker Aaron Traywick, CEO of Ascendance Biomedical, has died. Traywick was known for developing and self-administering CRISPR-Cas9 gene editing technologies – and even injected himself with an untested herpes cell therapy in front of a live audience earlier this year. The cause of death has not yet been revealed.



Get 'Em While They're Young

Pharmacy students take medicine safety lessons to school classrooms

Pharma companies and pharmacists go a long way to try and teach patients to be safe around medicines and to read medicine labels and leaflets. But let's be honest: human nature means that people often don't pay much attention.

At Robert Gordon University in Scotland, pharmacy students have found that children are very keen to soak up information about medicine safety, and so the university has partnered with local schools in Aberdeenshire to conduct workshops.

"Increasing use of social media and the accessibility of information means that children and adults have developed a wider understanding of some of the issues around medicine, but not everything on the Internet is correct so we need to communicate messages in others ways too," says Alyson Brown, Pharmacy lecturer at Robert Gordon University. "We tried to make it as fun and interactive as possible. We used placebo or pretend tablets for the pupils to count and label, and they measured liquids using different types of apparatus."

The agenda covers more than simply explaining why medicines are kept out of reach, by delving into the importance of the right amount of medicine, information on labels, expiry dates and storage of medicines. Some workshops have also included discussions about different types of medicines, such as inhalers that deliver drug directly to the lungs, and the production process for making medicines.

"There are already mechanisms in place to support medicines safety with children, but a lot of this is often aimed at the parent. If we can build things like this into education curriculums in a supported way, then we know we are getting the message to those most at risk," says Brown. "It's also been good for the pharmacy students, who learn to 'pitch' medical information at different levels to a diverse audience."

The big question is, should pharma get involved? Brown urges companies to consider reaching out to local schools. "Schools are always welcoming of initiatives like this where they can engage with external 'experts' and deliver on a key aspect of the curriculum, and I think companies have that expertise and can deliver interactive sessions which would allow children to experience some of the 'real life' science in the context of their learning," she says. "It's also a great way to promote science and encourage children to get involved."

Stay Ahead. Smart Risk Management

As supply chains become increasingly complex, collaboration between biopharmaceutical customers and suppliers is crucial for supply continuity and control.

By Dawn MacNeill

There is tremendous growth within the biopharmaceutical industry. Patient demand for life-saving and life-enhancing medicines is increasing; driving scientific and technological advances in drug discovery, development and manufacturing. As a result, biopharmaceutical manufacturers are intensifying their speed to market, increasing their capacity and optimizing their productivity. With rapid growth and geographic expansion comes an extended supply chain with more complexity and vulnerability to supply chain disruptions, such as natural disasters. At the same time, there is strengthened regulatory oversight of supply chains to assure patient access to quality drug products. To stay ahead, manufacturers and suppliers must collaborate to ensure continuity of supply.

Together, we must make "risk-smart" decisions to strategically balance the need to invest in capacity expansions and supply chain innovations to continuously supply customers with the right, high quality products in the right place at the right time with the need to continually mitigate risks and minimize supply disruptions. The routine, reliable supply of products depends upon a disciplined approach to supply chain management, from demand planning, materials/supplier management, production planning, and manufacturing to inventory management, warehousing, distribution, and logistics.

Meet the Expert: Aida Tsouroukdissian

I am Head of Demand Planning, Integrated Supply Chain Operations, at Merck. My team focuses on attaining an accurate demand and forecast to drive the right supply chain activities at the right times to meet customer requirements. We are responsible for securing and managing the global demand of our Process Solutions portfolio through a collaborative effort with our commercial, marketing and operations teams. The portfolio includes single-use systems, assemblies and components, aseptic, virus and TFF filters, chromatography, cell culture media, chemicals and more.

We use a Sales and Operations Planning (S&OP) decision making process to understand the market dynamics, drive production planning requirements, reconcile our demand-supply gaps, and inform our capacity plans and capital investments. The S&OP process is the basis of our monthly "consensus" demand plan for the next 18-24 months. On a quarterly and bi-annual basis, we review our portfolios with marketing to define a 5-year long range plan and a 10-year strategic plan, respectively.

This S&OP process has also been extended to some of our customers and critical suppliers directly, with whom we have partnered to increase transparency and reduce the risk of a supply disruption. These supplier-partner relationships are becoming more important to maintain service levels that keep pace with the anticipated ramp-up in the industry.

I find it very interesting and rewarding to collaborate with customers, suppliers and colleagues in this way. It's all about preparing for the future and mitigating risks!

To maximize resiliency, we execute a multi-faceted, "risk-smart" approach to supply chain risk mitigation. Leveraging years of experience, market intelligence, product and process knowledge, we proactively identify and prevent potential risks through effective capacity planning, business continuity planning, supplier quality management, change control management, disaster recovery planning, supply chain mapping and continuous improvement.

Data transparency and real-time, shared information between biopharmaceutical manufacturers and their suppliers is critical to effective capacity planning. An extremely crucial element of "risk-smart" mitigation is the provision of up-to-date, accurate customer forecasts. Ideally, forecasts will evolve from those currently based on single raw materials to the sharing of molecule BOMs (bills-of-materials) and critical products.

Another important element of "risk-smart" mitigation is business continuity planning (BCP). BCP is the process for identifying, preventing, mitigating and responding to supply risks for specific products. Prioritization of BCP's is based on a business impact analysis. During the BCP process, a risk priority number (RPN) is assigned to a product or a process that quantifies the likelihood of occurrence, likelihood of detection, and severity of impact. Risks above a certain RPN must be mitigated. Business continuity many include Disaster Recovery Planning for the site in which the product is manufactured.

Yet another important element to "risk-smart" mitigation is supplier quality management, which is designed to manage the quality of all procured products and services that directly and indirectly support manufacturing of finished goods. We categorize suppliers as critical, essential and non-critical. Although every procured product and supplier could be categorized as critical (after all, we cannot make the finished good without all the required raw materials), our categorization process considers the complexity of technology, sites impacted, country of origin, compliance and corporate social responsibility (i.e., REACH, conflict minerals and animal welfare), sales and more. The categorization determines the assessment frequency and method, such as audits.

Agreements, in which we are given visibility into customers' biologics pipelines and critical product needs, enable us to prepare for capital investments, reduce concerns over capacity constraints, enhance relationships with our respective suppliers, improve inventory replenishment, prioritize business continuity and change control decisions, and more.

Ultimately, collaboration is key to being more predictable and reliable with improved delivery metrics. In turn, biopharmaceutical customers can better meet the demands of their growing patient populations and comply with regulations, such as FDASIA.

Dawn MacNeill is Marketing Operations Manager at Merck.

Meet the Expert: Michael Donahue

I am Head of Production Planning, Integrated Supply Chain Operations, at Merck. My team focuses on our upstream supply chain from materials management to finished goods manufacturing. We're responsible for buying raw materials, managing inbound material flow, warehousing raw materials, scheduling manufacturing on the production floor and subsequently managing outbound material flow. As a result, my team is responsible for developing and executing the materials management program at several of the manufacturing sites. Essentially, the program is about evaluating and mitigating risks related to raw materials, and therefore, our suppliers.

In production planning and materials/supplier management, predictability is very important. When we commit to having finished goods available on a certain date, we want to be reliable in meeting that commitment. We work closely with our suppliers to ensure we have robust supplier quality agreements in place that include quality controls. For our critical suppliers, we use specialized tools to perform risk assessments and more importantly, collaborate with them to develop risk mitigation plans – reducing risk upstream greatly improves the predictability of our finished goods output downstream!

To mitigate supply disruptions, supply chain mapping is essential. We use an effective tool from a leading supply chain mapping/resiliency company. Some customers and several suppliers use the same tool, which provides alerts on relevant world events. For example, if a man-made or a natural disaster strikes a manufacturing site location of a supplier, we will receive an early warning event alert that enables us to act, such as decide to re-route materials from a different warehouse.

Of course, we have several other risk mitigations in place. We may have dual sources and/or dual suppliers. However, this isn't practical for many single-sourced raw materials. We would hold safety stocks – often at separate locations in case of a disaster.

I am very passionate about our upstream supply chain and making sure that we have suppliers who understand our customers' requirements. I think of raw materials as an enabler (or disabler). If you do an excellent job, nobody notices. But, if you are not doing a decent job, then everybody notices!

In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of pharmaceutical development or manufacture. They can be up to 600 words in length and written in the first person.

Contact the editor at: stephanie.sutton @texerepublishing.com

Old Drugs, New Computational Tools

Drug repurposing can benefit many areas of drug discovery – particularly rare diseases.

By Misagh Naderi, PhD Graduand, Computational Biochemistry Research Assistant, Department of Biological Sciences, Louisiana State University, USA.

There are about 7,000 rare or orphan diseases. But, perhaps counterintuitively, around 1 in 10 people are affected by one – so although the diseases themselves are rare, they are certainly not rare in terms of their collective impact! But as each of the individual conditions affects a small population, each represents just a small market. Unfortunately, this is what leads to these disease areas being neglected, as this small market doesn't justify the billion-dollar drug discovery process that big pharma needs to go through to find a new drug. But of course, the human impact is huge, and the psychological and financial burden of these diseases on society, patients and their family members is immense.

The pharmaceutical industry relies on basic scientific research that is performed by universities to provide leads, and we realized that we could help find a solution to the problem. It is well known that approved drugs can bind to multiple proteins – on average they can bind to as many as six targets – which is the cause of unwanted side effects; on the other hand, it also means that one drug has the potential to affect multiple targets, and therefore to treat multiple diseases.

This potential inspired us to devise a rational way to find the possible protein targets for drugs that have already been developed, using computational tools (1). Our Computational Systems Biology Group strategically bridges Biological Sciences and the Center for Computation and Technology at Louisiana State University, which allows us to use very powerful super computers to investigate biological questions on a large scale. With eThread, eFindSite and eMatchSite, three software tools developed in-house, we can predict the structure of proteins, annotate within the protein the drug-binding sites, and match those with known pockets that available drugs bind to – and subsequently figure out if the pockets match or not. The obvious usage for such a pipeline is drug repurposing, and applying this strategy to rare diseases to help with rational drug repositioning for such a vulnerable and underserved population was a no-brainer.

Structure-based drug discovery from scratch might not always be the most

"One drug has the potential to affect multiple targets, and therefore to treat multiple diseases."

effective path, but in the case of rare diseases it is a solid approach to finding a solution to a problem that has limited options. Keep in mind that we are not prescribing these drugs to patients; we are identifying proteins that are involved in a rare disease that can possibly be an ancillary target for a known drug. At best, our prediction can identify a drug that can be repurposed directly to alleviate the symptoms or treat a disease, but most probably it would be used as the first lead for drug discovery. We are hopeful about a few cases in the database that we have already published (2), and there are a few drug candidates that we are currently working on. We are also collaborating with experts in structural biology and biochemistry to test these drugs in vitro and provide the initial results needed to start the repurposing process. However, the project is an ongoing effort – as new information on protein structures is deposited into our database, and new proteins and pathways in rare diseases are discovered every day, we will continuously have new and better predictions.

Personally, I am excited to complete my PhD in Biochemistry and Master's degree in Virology and Veterinary Medical Sciences in May 2018, and I am looking forward to joining the biotech and pharma industry, as I hope to continue to be part of work that aims to improve human health. Governments incentivize drug discovery for orphan diseases, and the process of repositioning a drug is less cumbersome than gaining approval for a new one. The US FDA provides a fast-track process for treatment of conditions to fill unmet medical needs, such as orphan diseases. Research such as ours coupled with fewer complications in the approval process makes it less expensive to develop a product, which means profitability even with a small market size. Our work has the potential to streamline the repositioning process, and hopefully attract more pharma companies to the area of rare and orphan disease.

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It Doesn't Have To End In Tears

Rare diseases aren't the only field that can benefit from repurposing – companies should also consider breathing new life into old drugs for a much overlooked organ: the eye.

By Jeremy Drummond PhD, Senior Vice President, Business Development, MedPharm Ltd, UK.

Pharma companies are closely scrutinizing existing products to discover if they have activity for new indications, possibly through new routes of delivery. Repurposing comes with challenges as developers must go back to the drawing board to optimize the product for its new purpose, which may require a new formulation or delivery mechanism. However, repurposing also has many advantages:

- existing drugs are likely to have large portion of their non-clinical packages in place
- regulatory authorities offer simpler submissions (e.g., FDA via 505b(II) submission)
- greater understanding of basic biology in other therapeutic areas is uncovering overlaps in certain pathways and targets, especially in immunology and inflammation
- legislation and social media has made orphan indications more attractive.

Diseases of the eye are one area receiving increased attention from this approach, which is very good news for patients as not all ocular diseases have effective and non-invasive treatments. However, developing drugs for the eye is a significant challenge – the eye is a complex organ with unique anatomy and physiology, and it can be difficult to overcome its natural protective barriers. Repurposing an existing drug for an ophthalmic condition at least gives developers a head start rather than developing a whole new drug from scratch.

The desired site of action for drug delivery to the eye may be the cornea, conjunctiva, sclera, or other tissues of the anterior segment such as the iris, retina and ciliary body. If the back of the eye is the desired site of action, the blood retinal barrier is an obstacle to systemic delivery so a topical route may offer the best solution. Topical delivery to the eye is the least invasive and most flexible option compared to injection but the formulation has to battle a waterfall of tears induced by the drug's application and blinking to reach the site of action, which could be on, in or through the surface of the eye. The formulator has to anticipate that any permeation and penetration will be through the cornea, conjunctiva and the sclera. Often, this challenge is too great and developers turn to intravitreal injection (especially if controlled release of the drug could benefit the patient).

"Repurposing an existing drug for an ophthalmic condition at least gives developers a head start rather than developing a whole new drug from scratch."

Tears are one of the biggest obstacles to overcome when it comes to delivering drugs to the eye, but there are approaches that can significantly improve the chances of success. First, the formulation must be optimized for the desired target site. This may sound obvious but it is amazing how many companies fail to truly optimize their formulations. When repurposing a drug, developers should already have a lot of data about the characteristics of the API – and use these data to decide on whether a topical, systemic or periocular will be the best route of delivery. From there, formulators will need to look at product development with fresh eyes, beginning with pre-formulation work. For ocular delivery, it is imperative to consider how a drug

"With new models and growing knowledge around ocular formulations, there is a better chance that more pharma companies will consider repurposing drugs for the eye."

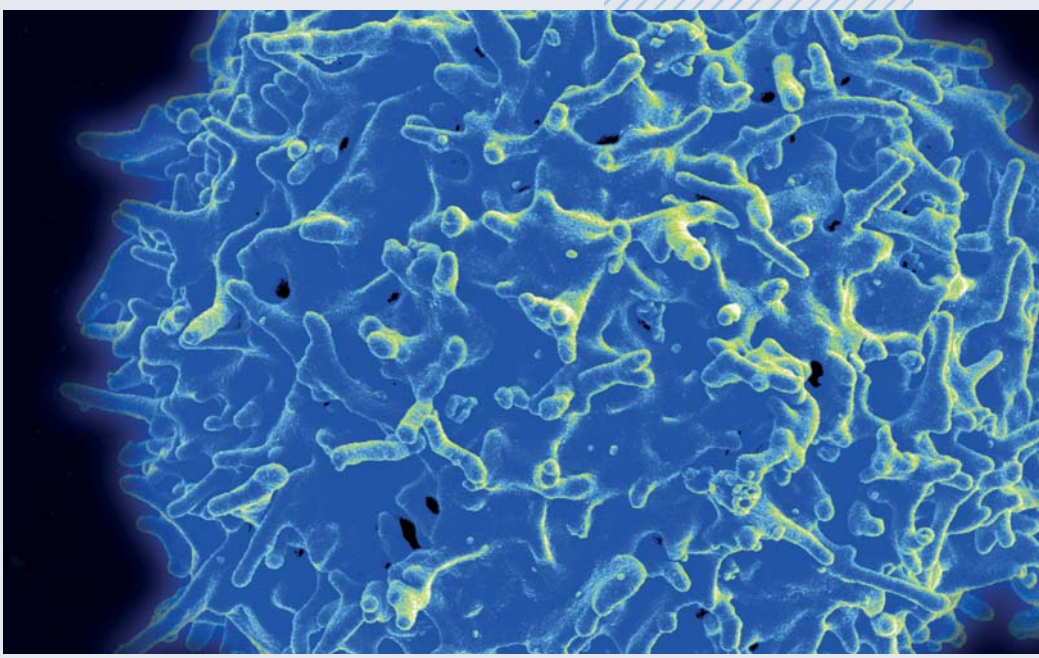
adheres to and penetrates corneal or scleral surfaces whilst in a heavy tear turnover environment. Specific excipients may be required that enhance a drug's adhesive properties, allowing sufficient time for drug retention and delivery.

Secondly, I strongly recommend identifying effective performance models and using these throughout the product development process to ensure your drug is reaching the correct part of the eye, and is bioavailable. You need to understand the pharmacokinetics and pharmacodynamics of your drug product before significant money is invested in clinical trials. Ex vivo models are developing rapidly for assessing drug permeation and penetration through the cornea/sclera, and can also consider the impact of tear flow. In addition, muco-adhesion models specifically tailored for corneal or sclera drug delivery can demonstrate sufficient retention on the eye surface.

These models are making drug development for the eye much easier and more attractive – and this is exactly what the field needs. Any eye disease can be extremely distressing for patients. If you have an eye disease, you don't care if it is rare or not – you want the best treatment. Drug development for the eye is challenging, but with new models and growing knowledge around ocular formulations, there is a better chance that more pharma companies will consider repurposing drugs for the eye. I believe the industry has a duty to ensure that patients smile, rather than end up in tears.

Industrializing Cell Therapy

We know that cell therapies work; now, we need to learn to manufacture them efficiently on an industrial scale.



Many see the growth of the cell and gene therapy field as the culmination of a healthcare revolution – a move away from one-size-fits-all approaches to truly individualized and personalized treatments. Over the past few decades, increased understanding of immunology and genomics has generated an unprecedented amount of biological information, which scientists are now beginning to translate into a new calibre of medicine. It's an especially exciting time for the field; the first two approved CAR-T therapies are already treating patients in the US and Europe.

"The complete response rates being seen for these kind of therapies are inspiring," explains Madhusudan Peshwa, Ph.D., Chief Technology Officer, Cell Therapy business, at GE Healthcare. "I am not aware of any small molecule drug or any biological drug having the ability to deliver such phenomenal outcomes for patients. This is stimulating the growth of the cell and gene therapy industry."

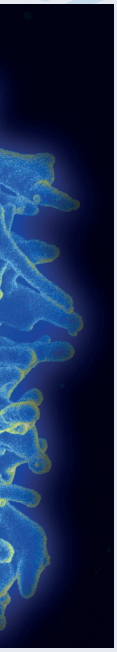
As the field continues to transition from the discovery stage to therapeutic reality, with further approvals sure to come, new challenges are emerging. The search for answers has quickly shifted from the mainly biological questions facing early-stage research scientists, to the challenges of industrializing and commercializing such therapies. "The industry is starting to realize that coming to grips with the manufacture of cell therapies involves a change in mindset and approach. With small-molecule drugs and biologics, manufacturers synthesize a batch of product in a "scale up" process, which often involves lyophilization, followed by conventional distribution and marketing," says Phil Vanek, Ph.D., General Manager of GE Healthcare's Cell Therapy Strategy. "Autologous cell therapies are different – for a start, they can't be lyophilized or formulated as a traditional tablet! But most of all, they require manufacturers to take a "scale out" approach. Every patient needs their treatment to be manufactured individually, so if a manufacturer needs to produce 5000 patient batches, or doses, a year, they must run each batch in serially or in parallel."

As the starting material for cell therapies is derived from patients themselves, Peshwa also points to another challenge: "There is a wide range of variability from person to person, in terms of the attributes and properties of the starting material, which makes it difficult to ensure that the manufacturing process always delivers within a defined range of attributes. We need manufacturing methods that can increase the reliability and consistency of the final product, no matter the starting material."

"Finding ways to remove risk from the process is one of the main focuses for cell therapy manufacturers."

Close and automate

Finding ways to remove risk from the process is one of the main focuses for cell therapy manufacturers. Cell therapies are a multi-step process involving collection of the material from the patient, transportation to the manufacturing site, manufacturing the product, and then shipping it back to the patient, but there are also dozens of other process steps in between – and when you are working with biological material and processing steps that require biological activity, the process does not discriminate between the cells of interest and bacterial contamination. The material must be treated carefully throughout – and the best way to prevent contamination is to automate a closed process.



"Historically, people have done whatever they needed in the clinical center to make these therapies happen, but given the expected growth of the cell therapy market, the industry will need to think more about an automated, industrial environment that can cope with larger patient numbers," says Vanek. "Manufacturers will need to consider consistent manufacturing and product quality, utilization of space, operational effectiveness and cost efficiency. Use of data – via smart systems based on digital and analytical technology – will also be key as it will offer insights into controlling manufacturing processes and ensuring product quality consistency. In time, we'll be able to use this knowledge to further automate processes, reduce the number of manufacturing steps and allow for aseptic transfers without manual interventions or a high degree of risk of exposure to the external environment."

GE has developed a number of tools and techniques that can be used to automate and close the manufacturing process – most of which are based on established flexible bioprocessing technologies, such as single use systems, or WAVE™/Xuri™ bioreactors. The word "flexibility" is crucial when it comes to cell therapies. Right now, the industry is learning many lessons about developing and manufacturing these therapies – and knowledge will only increase. In a few years, it is likely that processes will be very different, so deploying flexible technologies now, which have the capability to be adapted in the future, is a wise precaution. "In the future, I expect that we'll have much smarter methods to engineer our cells so that they are much more potent, which will change therapeutic doses and the amount of product that must be manufactured," says Peshwa. Does this mean that companies should hold back on implementing new technology? Not at all – there are huge opportunities for cell therapies today, and first movers will certainly reap the benefits.

"And there are a lot of fantastic solutions already available," says Vanek. "We've been approached by a number of customers looking to accelerate their path to market. They explain their basic process and then ask us to equip a factory for them. We've leveraged all of our experience gained with KUBio™ facility and our Enterprise Solutions to develop a solution for cell and gene therapies – it is basically a prepackaged factory ready to go."

But for cell therapies to truly be mass manufactured, there is also a need to make processing steps less specialized so that they can be carried out by non-experts. Given the cutting-edge nature of these therapies, many of the processes are comprehensible only to the specific scientists and technicians who worked on them at the clinical stage – and this small number of experts will not be enough to scale a therapy to thousands of patients. "When we work with customers, we look at their processes and investigate whether any steps can be simplified into sub-routines or made more efficient by removing certain steps. We also look at trying to introduce new technologies or methods that can accomplish those sub-routines as opposed to thinking about all the unit operations independently," says Vanek.

"Looking at the process workflow and identifying steps that have the highest risk, and then finding an effective way to automate these steps is a low-hanging fruit in terms of reducing the risk of contamination," adds Peshwa. "Right now the industry relies heavily on aseptic process qualification operator training and environmental monitoring in being able to deliver an unautomated manual process – and certainly this has been a success – but automation would bring about a significant reduction in cost of goods and help make product quality more reliable. Every time a human performs a step in a complicated process, there is the potential for a mistake to be made."

Finger on the pulse

Peshwa describes GE Healthcare as a company that likes to "keep its finger on the pulse". Indeed, the company is always looking out for technologies in the marketplace that could lead to more effective ways of engineering cells, enhancing their potency, and assessing the biological attributes or "fingerprints" of a therapy. "But most of all, GE Healthcare is not just a vendor, but a value-added partner," says Peshwa. "We work with customers to understand the product attributes that will drive clinical success and then we consult with customers through their stages to ensure they are optimizing their process. We'll also make sure that requirements from a robustness and scalability perspective are addressed early on – this is incredibly important to ensure smooth scale up."

Vanek adds, "GE has demonstrated real commitment to the field of personalized medicine and now is the time to move forward and help manufacturers overcome the challenges in the field. As an industry, we have more understanding of the causation and progression of cancer than we've ever had before, as well as developing a capability to effectively stratify patients in the future. Coupled with the genomics revolution, we are moving towards a whole new era of medicine."

I'm a (Biosimilars) Believer!

It's been a long winding journey, but biosimilars are finally starting to shake up the biopharma market. Their true potential remains untapped, however – hindered by market access and myths around safety. Here, four biosimilar gurus discuss successes and tackle the issues head on.

By Stephanie Sutton

What do you consider to be the biggest success stories for biosimilars in recent years?

Hoss Dowlat: I think the biggest success stories are the first wave of oncology monoclonal antibody approvals, trastuzumab (US and EU), bevacizumab (US) and rituximab (EU) and with extrapolation of all indications. These are long awaited and were developed by biosimilar leaders ahead of immunomodulatory products, such as infliximab and etanercept, but it proved very difficult to satisfy regulatory clinical requirements earlier.

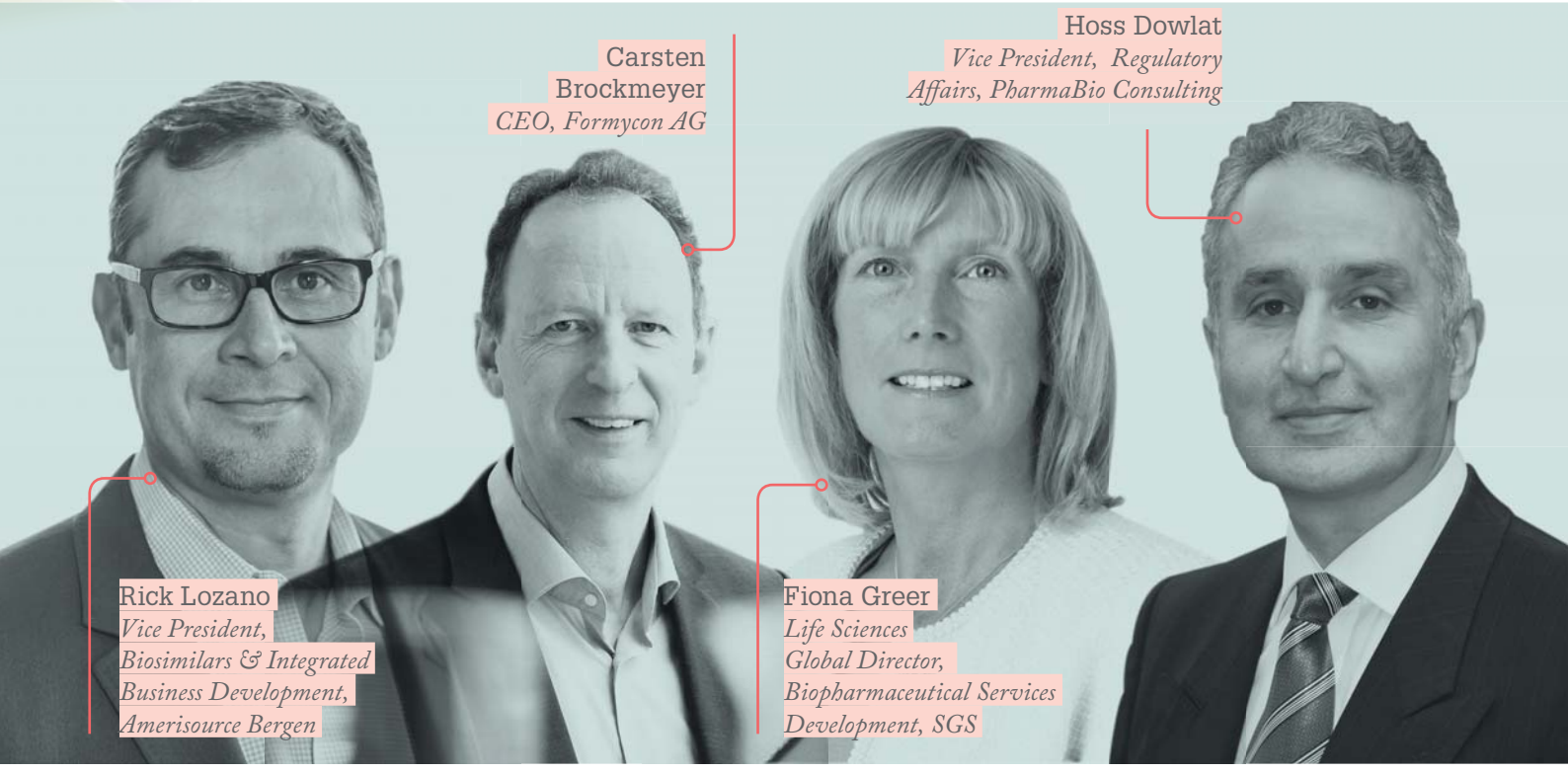
Carsten Brockmeyer: I agree with Hoss – and would, in particular, highlight the successful launch of the first European oncology biosimilar medicine, rituximab, which captured a 50 percent market share in Germany within 8 months.

Fiona Greer: Although there are inconsistencies among different nations, the EU overall has made great progress when it comes to the uptake of biosimilars. Over the past 10 years, we have seen the evolution of a science-based regulatory framework that has led to over 30 marketing authorizations in the EU and has driven development of biosimilar regulatory guidelines internationally. At the beginning of the "revolution," biosimilar versions of complex biomolecules, such as monoclonal antibodies, were considered impossible, but such molecules have now been approved. The prospect of biosimilars in oncology is particularly exciting, and the WHO is already working to prequalify biosimilars for cancer.

Rick Lozano: It's been a little different in the US – there are only a small number of approved biosimilars in the market and while there is no single "success story" that sticks out to date, there are elements of each that have been successful. For example, we are starting to see the first biosimilar in the US, Zarxio, gain market share as it has now found the appropriate channel strategy. We're also seeing each product learn from one another. I believe that when more biosimilars are approved for oncology as opposed to supportive care, there will be even more interest and adoption of affordable biologics, leading to more successful launches and greater insights.

It's important to remember that about a decade ago we saw the same challenges that biosimilars are facing today with the generics market, and, in that time, generics have been able to establish a good foothold on the market. Though we consider biosimilars to be a unique and distinct class compared to generics, the good news is that we see a similar trajectory with biosimilars as policy and reimbursement continue to advance.

The Gurus of Biosimilars



And what about low points for the industry?

HD: There have been some biosimilar development programs that have not gone as hoped, particularly for insulin. Today there is only one biosimilar insulin on the EU market and there have been a number of setbacks and failures for recombinant human insulins, immediate rHu-insulin, medium rHu-insulin and biphasic rHu-insulin. Many companies have also tried to develop a biosimilar PEG filgrastim, but this has not gone well. The regulatory barriers have exceeded expectations causing delays, while further development is leading to new filings of data with both FDA and EMA.

FG: It's certainly not been smooth sailing. There have been a couple of high-profile instances where GMP-related issues at some manufacturing sites have delayed approval for biosimilars until supplementary information is provided to the authorities. Instances like this can put the biosimilars industry in a negative light.

RL: Biosimilars have had many challenges coming to the US market, including struggles with channel, payer and pricing strategies. Though we've worked extensively with our manufacturer partners on all three, right now, we are finding that there is a need to focus on responsible pricing. Biosimilar manufacturers need to be careful when devising their pricing strategy, as collectively it is what upholds the market.

The manufacturing process for a branded biologic and a biosimilar will be different – what does this mean for the final product? And, ultimately, does it really matter?

HD: The manufacturing process for a branded biologic and a biosimilar can be very different; for example, different expression systems may be used in the fermentation process. In Samsung's biosimilar etarnecept, the expression system used for the originator molecule was replaced by a more modern approach using CHO cells – without any effect on safety, efficacy or immunogenicity. Voltropin (biosimilar somatropin) used a yeast expression system rather than bacteria, with no negative impact on similarity (Voltropin was ultimately withdrawn from the EU market, but this was for commercial reasons, rather than safety conerns).

In most cases, the same expression system is used to make justifying similarity easier. As the biological process is complex with many upstream and downstream processes, involving many reagents and materials and a range of equipment and conditions, the end product will never be exactly the same

– but it will be... similar! Based on my experience with many biosimilars from different sponsors, I've found that manufacturing and testing is often more tightly controlled for biosimilars – because they are so closely scrutinized by regulators – sometimes leading to narrower limits than the originator. The nonclinical and clinical results are the same, so I don't think it matters.

CB: Biosimilar medicines are 21st century biopharmaceuticals. The development of a biosimilar medicine provides an opportunity to introduce manufacturing innovations and state-of-the-art technologies. The reference products, in contrast, often tend to be locked in older process technologies. Significant advances have been made in biomanufacturing over the last two decades, resulting in the reduction or avoidance of non-desired materials, such as animal or human derived proteins, latex, silicone oil, or heavy metals, in biosimilar medicines. Safer, more user friendly drug delivery devices have also been made possible by technological advances.

Ultimately, the same chemistry, manufacturing, and control standards apply for biosimilar medicines and reference products. Approved biosimilar medicines in the EU and the US have demonstrated similarity to the reference product in terms of quality, biological activity, safety and efficacy, and thus provide a safe and efficient, state-of-the-art medicine to patients.

FG: What is not widely appreciated is the fact that because biologicals are "manufactured" in living systems, even different batches of the original product, itself, will not be identical. The originator, under specific regulatory oversight, may also modify their manufacturing process over the lifetime of the product, which may introduce slight variations in the range of product attributes. So, it doesn't matter if the biosimilar process is different, providing that the final product is demonstrated to have no meaningful differences to the originator.

RL: There are still large gaps in clinician understanding of, and confidence in, the manufacturing and approval process for biosimilars. The nomenclature – "similar" – perpetuates the myth that biosimilars are not as safe or effective as biologics. However, comparative studies leveraging research from innovator products are an accepted method of FDA approval. Additionally, FDA-approved biosimilars have proven to have the same mechanism of action as the innovator product. In fact, more than 10 years of biosimilars patient-use in the EU has shown no difference in health outcomes between patients who use a biosimilar and those who take the original branded biologic medicine.

WHO Wants to Put Biosimilars to the Test

The newest cancer medicines are considered expensive for developed countries – and they are completely out of reach for most low- and middle-income countries. In 2017, the WHO announced a pilot project for prequalifying two biosimilar medicines for cancer (1) – with the hopes of increasing access to treatment.

The WHO's prequalification programs ensure that medicines meet acceptable standards of quality, safety and efficacy – and their lists of prequalified medicines are frequently used by international procurement agencies and countries to guide their decisions around bulk purchases of medicines. WHO prequalification (launched in 2001) initially focused on treatments for HIV, tuberculosis and malaria, but the remit was extended in 2006 and 2008 to cover medicines for reproductive health, and zinc for managing acute diarrhea in children, respectively.

The decision to investigate prequalification of biosimilars was made following a two-day meeting in Geneva in 2017 between WHO, national regulators, pharma industry groups, patient and civil society groups, payers and policymakers. Discussions focused on how to increase access to biotherapeutic medicines. The first two biosimilar cancer drugs to be studied for prequalification are rituximab (non-Hodgkin's lymphoma and chronic lymphocytic leukemia) and trastuzumab (breast cancer). The WHO is also exploring options for prequalifying insulin.

According to the WHO, draft guidelines have been prepared and shared with stakeholders for consultation. "After the consultation process is over, WHO will issue an expression of interest letter inviting interested manufacturers to submit the two cancer medicines for assessment by WHO. We're expecting this to happen by the end of June, and then it will depend on the quality of the information submitted as to how fast WHO can assess the products, inspect the manufacturing sites and make a final decision on whether to prequalify or not," explained the WHO in an emailed statement.

Reference

1. *World Health Organization, "WHO to begin pilot prequalification of biosimilars for cancer treatment" (2017). Available at https://bit.ly/2vOcSCn. Accessed April 26, 2018.*

How have techniques and technologies for the manufacture, development, and analysis of biosimilars advanced in recent years?

HD: Some of the biggest advances have been seen in the analytical field – sensitivities have improved significantly and increasingly sophisticated systems continue to emerge. As Carsten mentioned earlier on, biosimilars are often able to benefit from new technologies. I see a lot of biosimilars using more modern processes compared with the originator.

CB: I agree that analytics have progressed significantly; the ability to analyze and characterize large glycosylated proteins has greatly improved. For example, significant advances have been made in high-throughput methods for glycan analytics, capillary-based protein analytics, and reporter gene cell assays.

Cycle-time reduction in process development has also been achieved by increased use of high-throughput platforms, including miniaturization, automation, and parallelization, in combination with single use upstream and downstream technologies. Some of these developments have improved our ability to screen large numbers of cell pools and clones, and speed up timelines.

FG: Over the last 20 years, advanced technologies have been developed for structural characterization of biological molecules. Indeed, the challenges of demonstrating biosimilarity have driven this development in part, with emerging novel technologies and improvements in older "classical methods". There is also a greater appreciation of methods that can link structure with biological activity or predict how the molecule might interact within the biological system; for example, HDX-MS. Essentially, regulators are looking for multiple orthogonal assessments to build a total profile of the molecule. In the US, the FDA has introduced the concept of "fingerprint-like" analyses.

Biosimilars have been available for years and yet articles are still being written in 2018 that question their safety. What do you think are the biggest myths in the field?

FG: The biggest myth is that they are less "pure, safe or efficacious" than the originator. Education that biosimilars are subjected to rigorous regulatory oversight, including clinical assessment, is needed to overcome these prejudices.

HD: There is no safety issue with biosimilars. In fact, my experience is that a biosimilar is often purer than the originator medicine and, more practically, more consistent batch-to-batch because the biosimilar manufacturer can benefit from recent technological advances, or new scientific understanding.

Regulatory scrutiny of biosimilars has been intense because they are a new class of product, but many have now accepted that there is nothing controversial about biosimilars. The FDA has established the practice of approving all first entry new biosimilars by presenting the case for safety and efficacy and extrapolation of indications to an external advisory committee and holding an associated public hearing, for an extra level of scrutiny and evaluation.

"There is no safety issue with biosimilars. In fact, my experience is that a biosimilar is often purer than the originator medicine"

CB: Biosimilar medicines approved in the EU or the US have the same quality, safety and efficacy as the reference products – this has been proven by more than 12 years of real world experience in Europe, with more than 700 million patient days experience under the control of the stringent pharmacovigilance systems. Patients can also be safely switched from the reference product to the biosimilar medicine, as many studies have shown. Providing educational information about biosimilar medicines to patients, physicians, and pharmacists is high on the agenda of many public and private organizations, and will increase understanding and acceptance of biosimilar medicines.

RL: We have a community oncology group purchasing organization – ION Solutions (an AmerisourceBergen company) – and we've had conversations with more than 5,000 community oncologists across the US. Certainly, biosimilar manufacturers need to educate more around safety, but I would also add that they need to look at other areas too. For example, biosimilars companies should match patient support services offered by the innovator, such as patient support programs.

Community oncologists do not move for price; rather, they look for support from their group purchasing organization contracts

What Regulators Want

By Bruno Speder, Head Clinical Regulatory Affairs & Consultancy at SGS

Unlike small molecule drugs, biosimilars are "manufactured" from living material and have a much more complex and intricate structure, so it is not as easy as classifying them as generic biologic drugs. This difference is acknowledged in the greater requirements of the various regulatory agencies for biosimilar approvals. The path to market for a biosimilar involves an abbreviated approval process, focused on proving "biosimilarity" to the reference originator product with physicochemical, biological and clinical data.

Head to head

The Chemistry, Manufacturing and Control (CMC) dossier is an essential part of the submission package for any pharmaceutical product to enter a clinical trial and, in a later stage, for an application for market authorization. For a biosimilar, the CMC part is even more important and the core of a biosimilar's dossier is a comprehensive head-to-head comparison of the biosimilar and the originator product, including points of difference between the two products, and how these will affect the product. The dossier must also include all details of the analytical (and other) methods that have been used to identify these differences (allowing the assessor at the regulatory agency to decide just how similar the two products actually are), as well as manufacturing details (including cell lines and sources of material), a description of the process control methods used, and information about how analytical data have been validated.

This head-to-head comparison is often made more difficult as data are rarely available for the originator products, which, in any case, may have changed through authorized manufacturing changes. In some cases, entire analytical exercises must be performed multiple times on different batches to enable comparisons to be made.

A comprehensive set of preclinical safety studies must also be carried out before any human volunteers or patients are dosed with the potential biosimilar, including in vitro assays and appropriate animal models, which are designed to predict whether those small differences may have an impact on safety or efficacy. Immunogenicity is a particular concern, but both in silico tools and in vitro assessments using animal tissue can be used to predict whether it is likely to occur in humans. Some regulations require animal immunogenicity studies be carried out before humans are dosed for the first time.

Clinical studies

For an originator product, phase I studies are typically carried out on somewhere between 30 and 48 healthy volunteers to establish safety; however, a biosimilar phase I study will involve anywhere between 120 and 200 healthy volunteers dosed with either the originator or the biosimilar drug. The trial will aim to detect differences in safety signals between the biosimilar and the originator product – and you need more participants to ensure the statistical relevance of results.

Study design should be agreed with the relevant regulatory authority to establish its acceptability and whether, based on the CMC dossier, the product may be considered biologically similar to the originator. Without this agreement, there is little point in continuing with development as it will be unlikely to gain marketing authorization via the biosimilar pathway. In addition to the phase I comparative safety study, a phase III study to prove equivalent efficacy is essential and the design of this study should be carefully coordinated with regulators to establish the necessary endpoints.

A biosimilar must have the same route of administration as the reference product and any changes to strength, pharmaceutical form or formulation, for example, will need to be justified to the regulators. Other changes, for example, optimizing the glycosylation pattern of the drug to improve efficacy, will not be compatible with biosimilarity. However, changes designed to improve safety, for example, reducing levels of known impurities or reducing immunogenicity, may not preclude a biosimilar decision.

A New Supporter

Initially, The American College of Rheumatology urged caution around the use of biosimilars. Information about the manufacturing process for a branded biologic is proprietary; a biosimilar manufacturer will not have access to the details of the process so how could they guarantee their product would be the same? It is now well accepted by the scientific community that biosimilars are safe, and in February 2018 ACR published a white paper, The Science Behind Biosimilars – Entering a New Era of Biologic Therapy (1), which aims to educate ACR members about and support the use of biosimilars.

"Increased real-world experience with biosimilars in Europe, new data including a prospective switching study (NOR-SWITCH), and increasing clarity around FDA policies (naming, switching) have all served to increase confidence in biosimilars," explains Doug White, one of the authors of the paper and ACR Board of Directors member at large.

The paper explains that a biosimilar and its reference product must have identical amino acid sequences and must be 'highly similar… notwithstanding minor differences in clinically inactive components' in many analytical assays. "The biosimilar must be equivalent to its reference product in clinical trials assessing pharmacokinetics/pharmacodynamics and clinical efficacy and must have comparable safety and immunogenicity to its reference product," says Jonathan Kay, Professor of Medicine and Timothy S. and Elaine L. Peterson Chair in Rheumatology at the University of Massachusetts Medical School in Worcester, and another author of the paper. "Thus, any differences in manufacturing processes between an approved biosimilar and its reference product do not result in 'clinically meaningful differences'. Patients receiving treatment with an approved biosimilar should not experience any difference in response than that which would be expected when using another lot of the branded reference product."

Despite the fact that biosimilars are safe and effective, uptake in the US has been slow. According to Angus Worthing, a doctor with Arthritis and Rheumatism Associates and chairman of the American College of Rheumatology's Government Affairs Committee, "Only two of the six FDA-approved biosimilars for rheumatologic diseases are available; the biggest obstacle is patent disputes and manufacturer decisions that prevent their use. One important long-term barrier is insurance coverage. Ironically, despite being priced 15-30 percent lower than reference products, we're seeing some biosimilars kept off formularies."

This appears to be a result of the US drug distribution system in which medication formularies are dictated by interactions between pharmacy benefits managers (PBMs) and manufacturers. The larger the rebate or price concession paid by manufacturers to PBMs, the more likely a drug will be on formulary, and a lower-priced drug may result in a lower rebate payment. "Biosimilars may be kept off formularies precisely because they are less expensive! This is paradoxical and may prevent biosimilars from realizing their promise of lower prices and increased access to treatment," says Worthing.

To help patients get better access to biosimilars, Worthing would like to see the FDA quickly finalize its interchangeability approval pathway so that manufacturers can perform clinical trials to demonstrate safety and efficacy of alternating back and forth between reference products and biosimilars. In addition, he believes it would be beneficial for Congress to reform the drug distribution system to create more transparency in the rebate system. Boosting the supply of biosimilars – including interchangeable biosimilars – and improving incentives to bring them onto formularies should improve access to biosimilars and help lower biologic drug prices.

Reference

1. *American College of Rheumatology, "American College of Rheumatology Recommends Biosimilar Use in New White Paper," (2018). Available at: https://bit.ly/2jhtZn8. Accessed May 1, 2018.*

to ensure they are able to stay viable in today's competitive and often unpredictable market. Clinical education about biosimilars may facilitate informed decision making, promote acceptance of biosimilars into clinical practice, increase accessibility, and expedite associated health and economic benefits.

What other big hurdles do you think face the field?

HD: There are huge data demands in terms of quality when it comes to developing a biosimilar; the FDA, for example, has precise requirements for analysis using statistical models – and this can be an insurmountable barrier for smaller biosimilar players. Also, both the FDA and EMA have requirements for phase III studies with at least one year of safety data. Major companies rely on their financial strength to conduct more studies and to generate more data than the minimum EMA or FDA requirements; partly, this is for exploratory reasons but also to fulfil what they perceive as the expectations of the medical community. However, the additional work escalates the cost of development and prevents some smaller companies from ever getting involved.

CB: There is no one hurdle facing the industry – there are several elements that can be addressed to further increase the uptake of biosimilar medicines. Right now, it is a bit like the early days of the generic industry when healthcare providers and patients were used to brand name drugs and were reluctant to use new generics. There is often rapid uptake today in some markets for newly launched biosimilar medicines, but not all biosimilars are equally successful. Awareness and education initiatives will help, and so will benefit-sharing models, incentives schemes, and, last but not least, improvement of tendering mechanisms.

FG: A major challenge for biosimilar companies is to make the biosimilar economically viable. The main "advantage" for biosimilar developers is that the regulatory process is "shortened" because a phase II clinical trial is not typically required. However, these regulatory pathways also require extensive, head-to-head comparability against the originator product. At the outset, obtaining batches of originator molecules is not easy and is very expensive as multiple batches are required for the biosimilarity exercise. That said, there are considerable financial incentives in that biological products tend to generate blockbuster revenues. If biosimilars can be marketed at a cheaper cost, they will attract considerable sales.

RL: I think we have everything in place to have a strong market for biosimilars, but the incentives that are crucial for the success of biosimilars, including rebates in the US, remain reserved for branded biologics. There is a tremendous need to find solutions that bring down healthcare costs. However, without sufficient biosimilar competition, uptake has been slow, and as a result, providers continue to choose biologics.

If you had the power to make one big change in the biosimilars industry, what would it be?

HD: Reduce the burden of testing by regulatory agencies – it would make it much easier for companies to develop biosimilars. I think we should carefully rationalize and justify all regulatory requirements. Harmonizing the FDA requirements with the EMA could also be beneficial. I find that the EMA sometimes has a lower regulatory burden, based on their significant experience with assessing and approving biosimilars.

CB: Carrying on from Hoss' comment, I would add that experience gained during the last 12 years in Europe has provided confidence in the ability to analyze and characterize small and large proteins. The need for large clinical studies will likely decrease in the coming years for a number of biosimilar medicines. Whether this will also include monoclonal antibodies will largely depend on the future progress in functional assays and pharmacodynamic markers.

For me, the big change I would make is to increase competition between biosimilar medicines and off-patent branded drugs by providing a level playing field with fair and equal conditions for all players.

FG: I certainly agree with the previous comments, but would also highlight the importance in educating the market as to the benefits of biosimilars. The biosimilars industry must step up efforts to market themselves as an industry group to stakeholders with the same dedication as originators – and this group must educate clinicians and patients about biosimilars to counter the "negative" image. Many individual companies, and some industry organizations, do this already, but if forces and resources were combined, the message would have greater reach.

RL: For significant cost savings to happen, we need to dramatically expand patient access and bring more biosimilars to market. I would change one of two things. The first option is to either shorten the length of biologic patents or change the laws to shorten the length of the exclusivity period. We see products in the immunology space that have several hundred patents on one product with four or five indications, and companies can hang on to these patents for a significant amount of time. The second option is to allow biosimilars to come to market without the 180-day notice period to innovators in the US, which would help eliminate a patent dance and time (and money) spent on litigation.

A Vendor's View

With Nigel Darby, Advisor, GE Healthcare Life Sciences

On market competition

There are over 100 projects to deliver biosimilars for the top ten biopharmaceuticals that have gone off-patent or will be going off-patent in the next few years. Participants range from small regional start-ups, all the way through to major pharmaceutical manufacturers. Perhaps surprisingly, some companies with strong portfolios of original molecules, such as Amgen, have also chosen to develop biosimilars programs. Biosimilar manufacturing is highly competitive, with the most popular originator molecules potentially spawning over 20 biosimilar projects each. This intense level of competition creates significant uncertainty in manufacturing capacity demand and the dimensioning of facilities to achieve it.

With so many biosimilars competing for the same market, it's obvious that the first products launched will have a significant advantage. Given the level of competition around certain molecules and therapeutic indications, it's impossible to believe that all these projects can be commercially successful. For example, in terms of the latter, I'm guessing there may be twenty different biologics targeting psoriasis by 2020 compared with perhaps just three ten years ago…

On making biosimilars

Biosimilars need to be as "similar" as possible to the original drug in molecular, therapeutic and safety characteristics. This is a challenge with something as complex as a biological molecule, so careful control and characterization of the production process is key – and tools that allow comparison of originator and biosimilar molecules are of major importance. Achieving acceptable similarity to some of the "subtleties" of originator molecules, such as glycosylation profiles, can be particularly challenging, requiring a significant focus on cell culture and media development.

To gain a competitive advantage, cost-effective manufacturing of biosimilars is important. In particular, there needs to be a strong focus on maximizing manufacturing plant utilization and productivity, as these are major drivers of manufacturing costs.

On manufacturing strategies

Many biosimilars are intended to be manufactured in emerging markets, which may not have appropriate manufacturing infrastructure available or the necessary expertise at all levels (managers, scientists, process developers, manufacturing operators) to develop biopharmaceuticals. Even basic requirements that are normally taken for granted, such as stable power and water supplies, may be a challenge in certain countries (that said, many manufacturers in markets such as China have the stated goal of selling their products to Western markets, making them sensitive and perhaps conservative in terms of satisfying Western regulators).

Companies wanting to get into the biosimilars market need

Nigel's Dream Biosimilars Facility

It would be a multi-product facility, given the commercial uncertainty that may surround an individual product, as well as the fact that the ability to drive multiple products through a facility is a key requirement for economically efficient manufacturing. The facility would need to be the right size – appropriate for the likely market demands and risks, but future proofed so that capacity can be rapidly expanded if drug demand is sufficient.

There would be maximum flexibility in terms of the types of products that could be handled and production would need to be easily reconfigured. I would like an open architecture "ballroom" type facility that enables flexibility in deploying equipment.

The costs for low added-value activities, such as cleaning and maintenance, would be minimized, and uptime for manufacturing maximized. Also, technology would be adapted to intensify all parts of the process, reducing both upstream and downstream cycle times to increase batch throughput.

"Although single-use and modular manufacturing methods have many benefits, there is still an active debate as to the 'right way' to manufacture biosimilars."

to carefully consider their manufacturing strategy – and perhaps look to using flexible technologies, such as single-use systems and modular systems, that can get manufacturing operations up and running quickly, with reduced capital investment. Overall, costs shift towards variable costs (in other words, costs only incurred when the drug is manufactured) compared with traditional infrastructure, where fixed and capital costs predominate and are incurred irrespective of whether manufacturing is taking place.

Single-use technologies are also very appropriate for the required levels of product output of a biosimilar. For example, predominantly single-use modular facilities can deliver amounts of monoclonal antibody in the 20-1000 kg range, which is appropriate for serving individual countries or regions and fragmented markets. If a drug proves to be particularly successful, increasing supply can be achieved by building further manufacturing lines – this is a comparatively cheap and quick process with modular type facilities based on single-use technology. If there is significant commercial uncertainty (the case for many biosimilars), it often makes sense to launch the product from the smallest, lowest capital cost facility possible, and then scale out, if the molecule is successful.

Logistically, modular facilities are readily deployable in emerging markets in a rapid and cost-effective manner, whilst at the same time achieving high quality standards. The bulk of the construction and fitting out can be carried out remotely and be assembled quickly on top of a foundation with basic services at the final location in a period of a few months.

On single use versus stainless steel

Although single-use and modular manufacturing methods have many benefits, there is still an active debate as to the "right way" to manufacture biosimilars, with many arguments suggesting that large, well-utilized fixed infrastructure can also deliver favourable economics. The key is high facility utilization, targeting big products for a global market, especially if it increases use of existing infrastructure. This is the strategy adopted by companies such as Celltrion and Samsung, and it is worth noting that the Remsima biosimilar is manufactured in a more traditional type facility. The choice between "big traditional" and "single use" (modular) depends on the market, risk appetite and commercial expectations.

On the future

Biosimilars have been around in Europe for many years and are already a significant part of the market. The first biosimilar on the US market, Zarxio, was introduced a couple of years ago and has been steadily gaining market share. But I think the big question is how successful monoclonal antibody biosimilars will be. Uptake of Remsima, a biosimilar of Remicade, has been strong in Europe, driven by aggressive pricing. The development of the mAb biosimilars market in the US is expected to be slower; though, given its novelty, it is hard to assess. Will payors and patients drive uptake in the absence of the strong government influence that has been so important in Europe? And exactly how much discount (compared with the originator) will be required?

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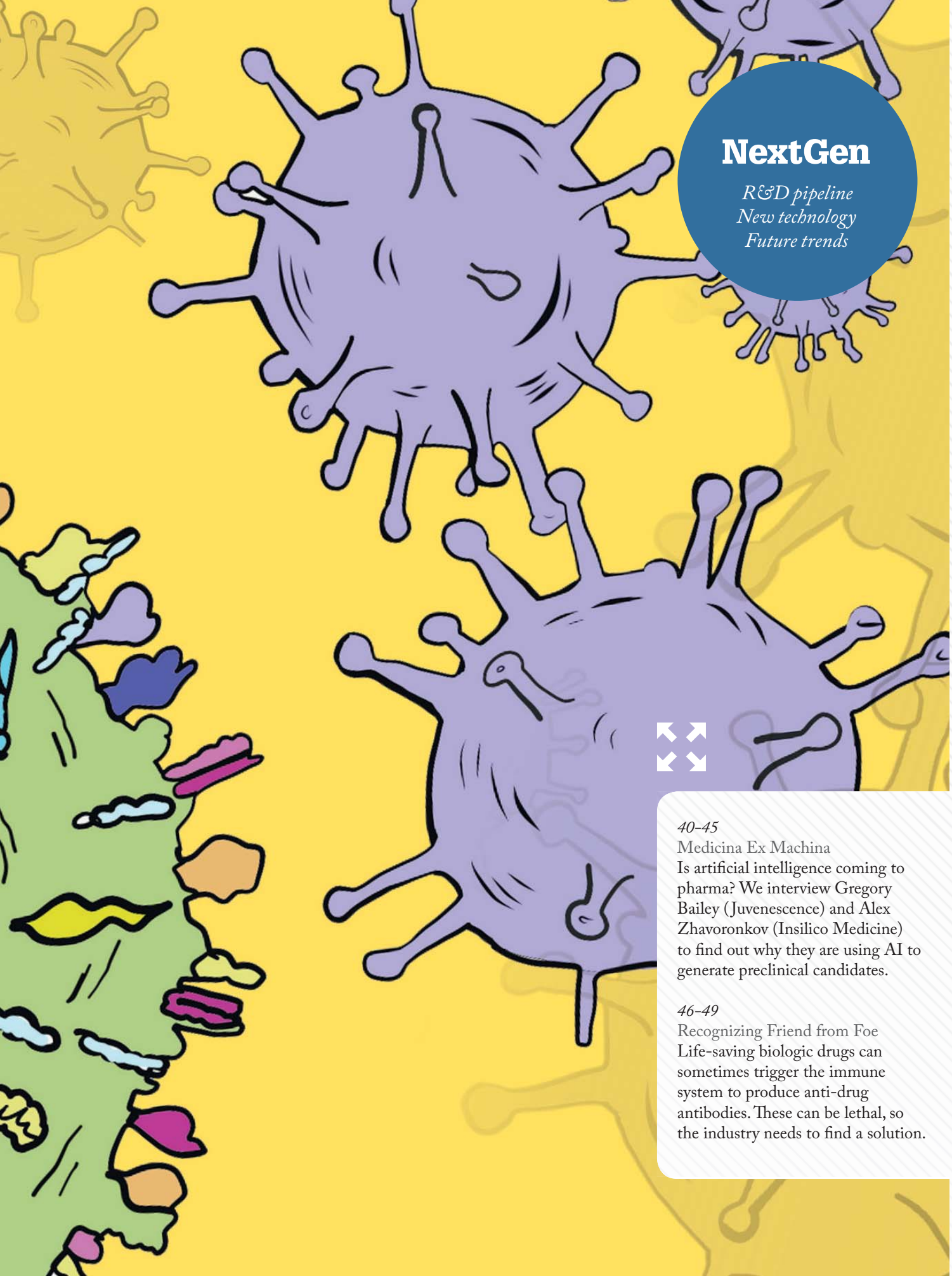


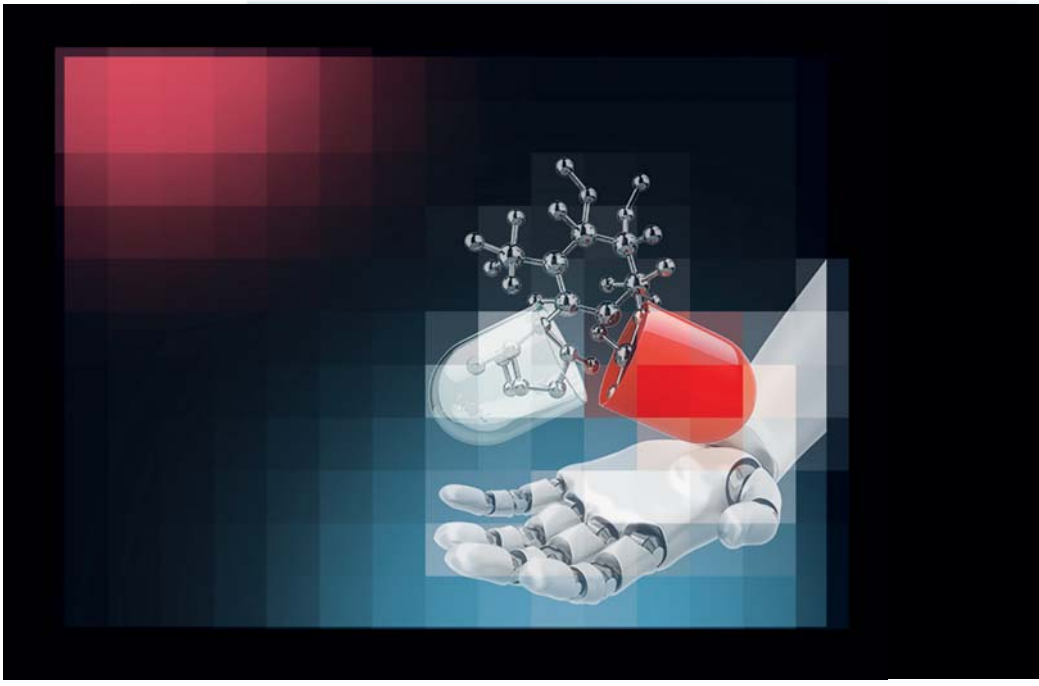
NextGen

R&D pipeline
New technology
Future trends

Medicina Ex Machina

The sci-fi inspired concern that artificial intelligence will one day rule the world is (mostly) unfounded, but it certainly could have a huge impact on drug discovery.

By Roisin McGuigan



Traditionally, pharma companies have been skeptical about the promise of artificial intelligence (AI). But with its potential to bring powerful new tools to the often slow and expensive drug discovery process – and its ability to predict which drugs are most likely to successfully run the clinical trial gauntlet, pharma companies are waking up to the fact that it really could be the future.

In 2017, a collaboration began between Insilico Medicine, an AI company specializing in deep learning for drug discovery, and Juvenescence – a company focused on investing in treatments for age-related diseases and longevity. The aim of the partnership? To find out if AI techniques could enhance drug discovery in the tricky area of age-related diseases, including dementia, diabetes, and cancer, as well as the aging process itself.

In 2018, the companies announced that a handful of promising molecules generated by Insilico's deep-learned drug discovery engines would be heading into preclinical and clinical development, headed by Juvenescence AI, a joint venture between the two companies. Juvenescence AI is also seeking to independently develop its own AI engine focused on accelerating the clinical development of novel drugs. Here, we speak with Gregory Bailey and Alex Zhavoronkov – CEOs of Juvenescence and Insilico Medicine, respectively – to find out more about the collaboration, and the potential of AI.

What drew you to AI?

Gregory Bailey: Juvenescence is a relatively new company – but we are fortunate to have attracted a team of seasoned drug developers from big pharma and biotech. Having seen millions of compounds sent through high-throughput screening to generate a single lead, our team was captivated by the idea of replacing a time-consuming and wasteful process with AI-driven compound development. The potential to generate lead compounds without high-throughput screening was enough of a draw for us to want to partner with Insilico, but we were even more excited by the prospect of using AI and machine learning techniques to parse through existing genetic and transcriptomic data to identify exciting new targets for drug development.

Alex Zhavoronkov: There is a lot of hype around AI, and most of it is because of recent advances in deep learning and deep reinforcement learning. AI techniques started outperforming humans in many tasks starting in 2014 and 2015 – examples include superhuman image recognition, autonomous driving, and the famous defeat of the human champion of the ancient Chinese board game, Go.

Pharma is perhaps one of the most inefficient industries, with about 90 percent of new drugs failing in clinical trials. The industry spends over $150 billion annually on research and only 40–50 drugs are approved every year. However, pharma companies also generate enormous amounts of data that could be used to train AI systems. We were very impressed by the results of deep learning in images; specifically, Andrej Karpathy's work on computer vision back in 2014 – and now powering the Tesla's Autopilot project. He demonstrated how deep neural networks could describe pictures in natural language. Some of these descriptions were better than mine. And when he

"There is a lot of hype around AI, and most of it is because of recent advances in deep learning and deep reinforcement learning."

showed these results at the NVIDIA GTC2015 conference, where Insilico also presented, I decided to invest everything we had into deep learning for drug discovery. I co-founded Insilco Medicine with the ultimate aim of harnessing available data to minimize the need for animal testing and clinical trials by using AI and deep learning to identify new therapeutic compounds and predict biological activity. Back then (this was around 2014), nobody in pharma was using deep learning and it was extremely difficult to explain what we were doing to big companies!

In 2015, I was invited to give a talk in Boston at a closed-door immune-oncology (IO) event organized by a big pharma company, which wanted to understand why it missed the IO revolution and how it should move forward. All of the research executives were there, and for the first time I presented our work in deep learning. No one was interested except for the executive editor of Molecular Pharmaceutics, Carston Wagner, who invited us to submit a paper. It is now an extremely popular paper with an Altmetric score over 750. But the big pharma company did not follow up on the meeting, so I guess they missed the boat in deep learning just like they missed it in IO. Ironically, we do a lot of work in IO with deep learning nowadays!

How does AI work in drug discovery?

AZ: The most difficult part of the application of deep learning to drug discovery is the pace of progress. In deep learning, there are several papers published every week with ideas that can be incorporated into the drug discovery pipeline, and our team is coming up with new ideas on a daily basis. If we were to turn our pipelines into a software product, in a month it would be obsolete. That's why we keep all stages of our pipeline in a flexible "Lego-like" mode and run the entire pipeline only when we absolutely need to churn out new targets and molecules for partnering and licensing.

The current pipeline starts with deep learned and pathway scoring algorithms applied to massive "omics" databases for target identification. We use generative adversarial networks (GANs) to reconstruct the missing or erroneous values or to generate diverse data sets that we may be lacking. We heavily rely on the predictors of disease state, or in the case of aging, age of the patient, where we extract the most relevant targets and pathways of the disease or aging. We then engage a second part of our pipeline, where we look for the molecules that may effectively inhibit or modulate some of these targets or pathways.

We do this in three ways:

- Screen the existing molecular libraries for molecules that are likely to bind to a specific target.
- Screen for molecules that can effectively reverse a disease pathway signature.
- Generate completely novel molecules that can bind to a specific target using our GANs. GANs are trained on multiple data sets to "imagine" molecular structures that have the characteristics of a good drug. We also introduce a reinforcement learning (RL) component, which helps build the molecules with a specific objective. We have a large zoo of these GAN-RL models and we are building new ones almost every week.

The most promising leads are then scored using a predictor of clinical trial outcome. For disease areas with sufficient data available, we created predictors of success or failure using the "omics" data and the structure of the molecule. The highest-scoring molecules are then synthesized and tested experimentally.

How did this collaboration come about?

AZ: We met the Juvenescence team when Jim Mellon, one of the core founders of Juvenescence, was doing research for his book "Juvenescence" – which discusses the science of longevity. This is where we connected, because we were also interested in developing biomarkers of aging and linking the targets implicated in aging with disease. Jim is often referred to as the "British Warren Buffett" (even though he may not like it!) because he makes some bets very early on, and these bets often turn into multibillion-dollar businesses. Gregory Bailey has a similar track record in the biopharmaceutical industry, so it's a good combination. We really liked the team and worked very hard to establish this collaboration. Juvenescence invested in Insilico and now has the right to license up to five of the best molecules discovered using our deep learning engine annually.

GB: Jim Mellon introduced Alex to

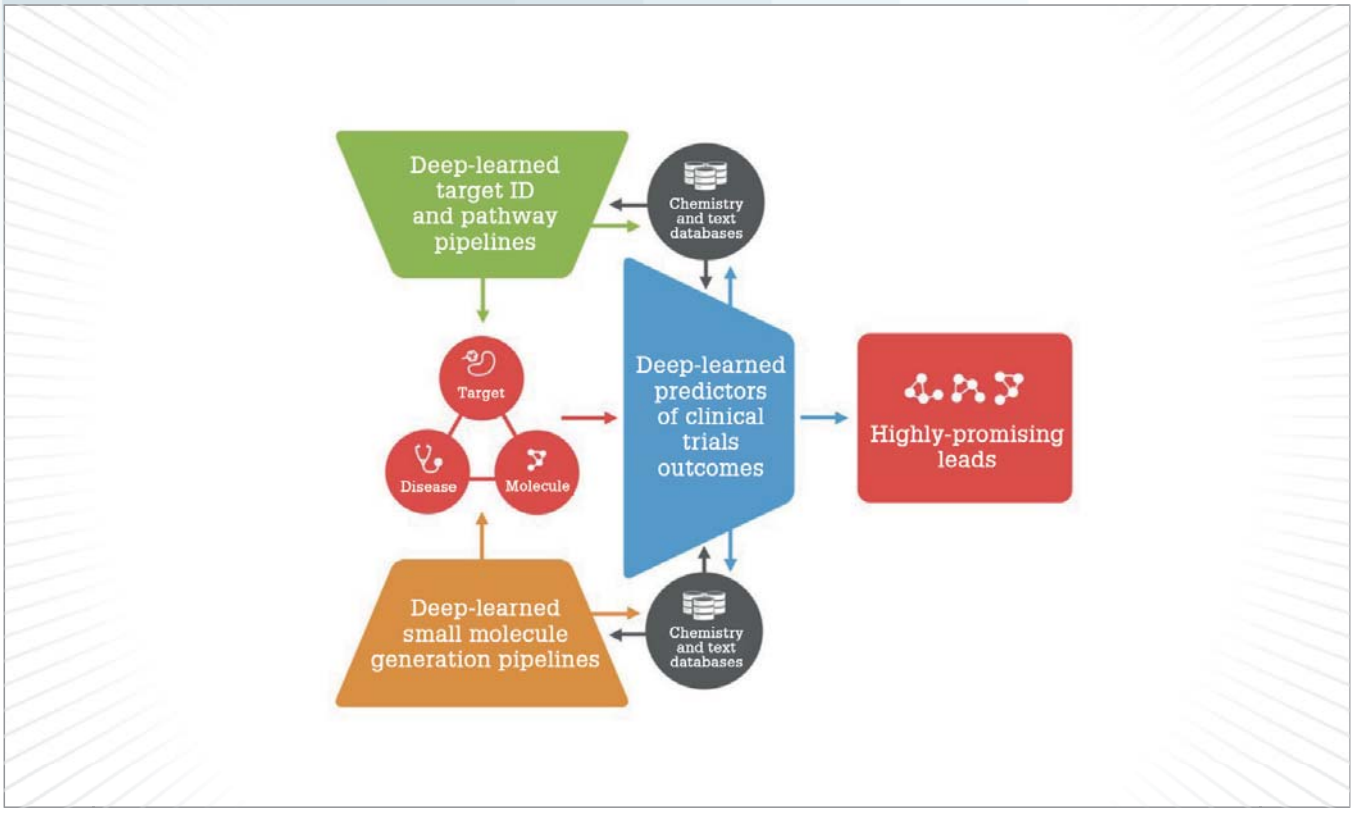


Figure 1. Integrated top-down and bottom-up target ID and drug discovery pipelines.

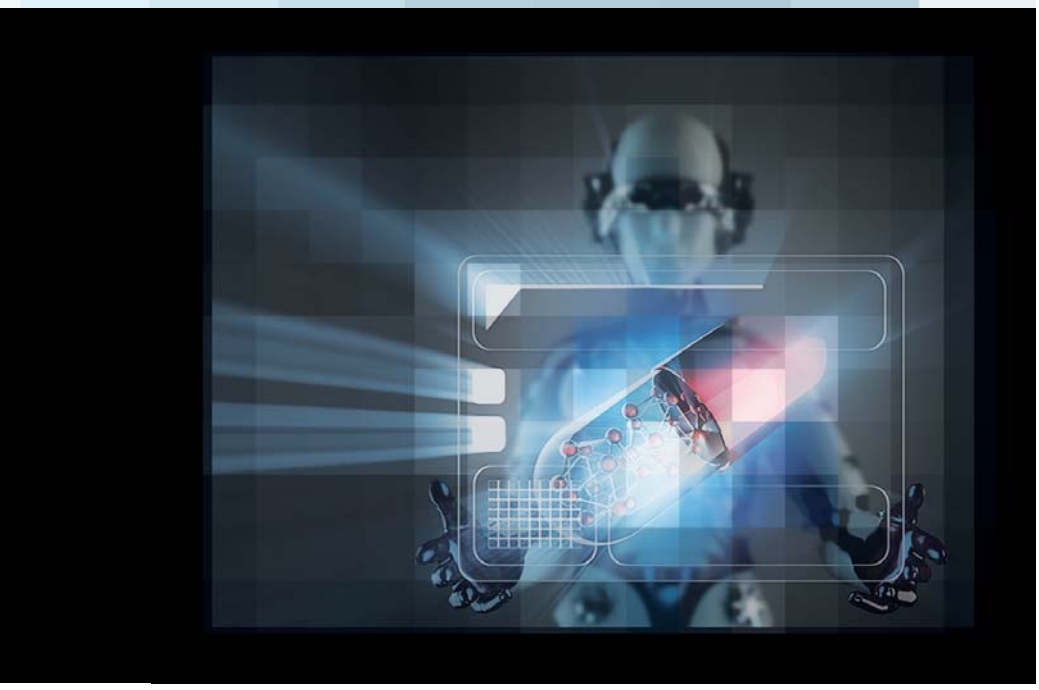
the rest of the Juvenescence team, and we were fascinated by the potential of Insilico's drug discovery engine to shorten the time between target identification and lead candidate selection. We decided to make an investment into the company and to create a joint venture to develop five drug families per year, playing to our strength in drug development – and Insilico's strength in drug discovery. This led to the creation of Juvenescence AI, a subsidiary of Juvenescence Limited dedicated to combining advances in AI with our classical techniques, to develop compounds sourced from Insilico Medicine's drug discovery pipeline and take them through to clinical proof-of-concept.

The team behind our company have an extensive track record in drug development and biotechnology investment, and by using AI to massively reduce the long and expensive drug discovery process we hope to eventually develop drugs to treat both aging itself and diseases of aging including diabetes, dementia, cancer, and respiratory disease.

What advantages does an AI approach offer?

GB: AI approaches to drug discovery offer three major benefits: enabling drug discovery programs against targets for which no high-throughput assay is available, reducing time to lead candidate selection, and identifying new targets of interest. How we apply AI depends on the task; in some situations, it is used to identify a target of interest that can be explored using known biological tools, and in some situations it can generate compounds that are predicted to interact with a given target. Our goal is to build a tight feedback loop between Insilico's AI engine and the biological experiments conducted based on its output.

AZ: When you really delve into AI and begin to understand how to combine AI tools with advanced machine learning and bioinformatics, you should be able to look at complex diseases and narrow them down to a set of actionable and druggable targets. It can also help us to understand the population-level response and generate new molecules with a specific set of characteristics for the individual targets using GANs and RL. Such generation was not possible just two years ago, as GANs are a very new concept – we were the first to publish and validate the applications



"We are also interested in investments that use AI technology to solve other problems in the pharmaceutical industry, particularly in drug development."

of GANs in both medicinal chemistry and biology (1, 2).

I really believe that our AI pipelines are among the most comprehensive in the industry. AI can be used for a top-down approach and can work with multiple omics data types to identify targets for individual diseases, and a bottom-up approach to identify or generate the best molecules for individual or multiple targets. We can then use AI to assess the probability of passing the clinical trials for some of the molecules (see Figure 1).

Why focus on aging?

GB: I think that finding therapeutics for aging and age-related diseases presents us with the opportunity to have the most dramatic effect on the largest population – potentially 7.8 billion people. We are also interested in investments that use AI technology to solve other problems in the pharmaceutical industry, particularly in drug development. AI is a very exciting new tool that gives us the ability to do work that is too time consuming or even impossible for a human. It can also assist us with many of the issues we confront in drug development, such as viable drugs that fail due to a spuriously high placebo effect, or improper patient selection for clinical trials. AI will help drug developers sort out these problems, and therefore have an effect in many different areas.

AZ: I personally have always been fascinated by the idea of extending healthy longevity, but aging is an extremely complex and multifactorial process. As a result, we have taken a wide view of the field, with a variety of projects and collaborators. Aging is also a very important component in many diseases and it is extremely important to study it in both biomarker development and drug discovery, as people of different biological age simply do not respond to therapies in the same way.

We intend to publish many "firsts" this year in multiple areas, ranging from cancer immunotherapy to novel molecular structures generated using AI – and we've already started. For example, we were the first to publish a deep-learned predictor of human biological age using simple and inexpensive blood test results. So far we have three papers describing this methodology, and we use it internally on other data types like gene expression and genomic data (3). We were also one of the first to publish on the applications of the adversarial autoencoder (AAE), a form of GAN, in a peer-reviewed journal (2). We submitted in June 2016 and published in December 2016, as it took two months to find the relevant reviewers. In the meantime, another group, led by Alan Aspuru-Guzik from Harvard published the application of the variational autoencoder (VAE) in October 2016. So we can say that we were first to submit, but they were the first to publish. The Aspuru-Guzik group is our main competitor in this area – and a pretty formidable one at that! We have a lot of respect for their team.

"We can use AI to assess the probability of passing the clinical trials for some of the molecules."

What successes have you seen so far?

GB: In terms of drug development, our collaboration has only just begun, and we are in the process of learning about the strengths and limitations of the AI engine. Similarly, Insilico is learning how to interact with the culture of biotech drug development. We have selected a family of geroprotective compounds for development as our first license, and we are also seriously exploring the biology behind four other potential programs.

AZ: So far, we have had many proofs-of-concept, some of which are published. We were also involved in another collaboration in which we applied our AI methods to the development of nutraceuticals, which helped us learn how to work with large population data. We have also had multiple pilots with large pharma companies, and some of these will be published in the near future. But I would consider our real success the partnership with Juvenescence – the successful licensing of our compounds is a major milestone for us! But in pharma, the only outcome that you can truly call a success is the completion of a phase III clinical trial for a blockbuster drug – and we're still quite far away from that!

What's next?

GB: Our goal for Juvenescence AI is to build a continually-renewed pipeline of therapeutic candidates. Acknowledging the odds of drug development, we would be delighted if two compounds achieved clinical proof-of-concept in an aging-related disease every year!

AZ: We plan to provide Juvenescence with safe and effective molecules at the early preclinical level that can potentially turn into new drugs targeting both age-related disease and aging itself. Together, we aim to become the core of what will be called the longevity biotechnology industry. The current pharmaceutical model is focused on treatment and, initially, we will need to play by this rule. But in the future, we hope to prevent diseases from occurring, and to help people live longer in a healthier and more youthful state.

How do you think AI will alter the pharma industry as it advances?

GB: Although AI has the potential to open up new landscapes of targets, drugs against these targets will need to fit into the current therapeutic development paradigm. We think the key near-term structural change that AI will bring to drug discovery is a reduced need for the capital-intensive, high-throughput screening process. The collection and collation of more biological data, however, and maturation of machine learning and AI techniques will enable more profound changes to the therapeutics industry, but the structure of the pharma industry is largely a product of its regulatory environment. I hope that as AI techniques prove themselves, regulators will embrace them for drug discovery and development. We assume that for now change will be slow, and we will need to see multiple successes before regulatory processes are updated.

I firmly believe that AI has unique potential to open up new drug targets that humans would not have conceived of, which have the potential to change the therapeutic compendium. AI is an amazing tool; it is not yet a stand-alone solution to all problems in medicine and drug development but certainly it can help humans deal with the extraordinary complexity of biological systems and help us to solve some of the biggest mysteries and challenges in biology.

AZ: Many large pharma companies are still saying that AI is overhyped and we need to slow down. They claim that the AI field is overpromising and will under-deliver, and refer to similar claims made by computational biologists and chemists in the 1990s. Some older-school computational discovery scientists and even some younger academics from the top institutions, who are just entering the deep learning field and want to make a name for themselves, often refer to how easy it is to fool deep neural networks, and how difficult they are to interpret. These people often support each other at conferences and in the press claiming that AI is overhyped and that pharma companies should limit their investments in this field. After the driverless Tesla demonstrations they switched gears and started making arguments for the human-machine union, where deep learning techniques can act as useful tools, while still claiming that AI is overhyped.

My response to these people is simple – AI in drug discovery is not overhyped. In entertainment, robotics and consumer businesses, investors are pouring billions into AI, but this is not the case in the pharma space. Our company struggled to fundraise until 2017, and even after the investment we remain very lean and I do not receive a salary. Many other companies are finding it hard to fundraise as well, and pharmaceutical companies are trying to build internal expertise in

this area but failing to attract the right talent. My guess is that in 2016 the total capitalization of the entire AI for drug discovery market was under $300 million with the exception of one company, which managed to get into unicorn territory.

The CEOs of the top pharma companies do not yet see AI impacting their bottom lines, at least on the discovery front. These people are busy with the products they have on the market and with what can be acquired in late-stage clinical trials. But considering the potential, the results we see in the lab and the lag between virtual and real experiments, promoting AI in the pharma space and educating executives on the differences between traditional machine learning and next-generation AI is a very logical thing to do.

I personally think that AI will transform the way we discover drugs, and diagnose and treat diseases. To quote Bill Gates, "We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten. Don't let yourself be lulled into inaction." I think we need to act now, and act fast.

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Alex Zhavoronkov is CEO of Insilico Medicine, Inc, a company specializing in the development of next-generation artificial intelligence and Blockchain technologies for drug discovery, biomarker development and aging research.

Gregory Bailey is CEO of Juvenescence Limited, an investment company focused on developing therapies for anti-aging and age-related diseases, which will be using AI to augment its drug discovery and drug development programs in partnership with Insilico Medicine.

Recognizing Friend from Foe

The immune system scrambles into action when a foreign entity is detected, but not all foreign entities mean harm. New solutions are needed to teach the immune system to recognize biological drugs as partners rather than plunderers.

By Werner Cautreels

The human immune system is an incredible defense mechanism that has the ability to interrogate and respond to any harmful entity (or 'antigen') that it is exposed to. When we are exposed to viruses, our dendritic cells sample the particles, process them, and then mobilize the immune system into action, resulting in the production of antibodies against the virus. The same mechanism has been exploited for vaccination, of course.

But the immune system also has a darker side – antibodies can form in response to anything deemed as 'foreign,' including biological medicines that are intended to improve – or to save – the patient's life. A well-known example is coagulation factor VIII – a clotting protein required by patients with hemophilia A. In a surprisingly large percentage of patients (over 30 percent), the immune system treats factor VIII as if it were a harmful entity and starts to make anti-drug antibodies (ADAs). This often results in a loss of efficacy and may also cause severe hypersensitivity reactions, including anaphylaxis.

Arrested development and allergic responses

When I started my career, most therapeutics were small chemical molecules, but today the focus has shifted to biologics. The immune system does not react to small molecules, but it can often react to biologic drugs, such as proteins, monoclonal antibodies and enzymes. A surprisingly large number of biologics already on the market induce the production of ADAs in many patients. Not only can ADAs reduce drug efficacy and modify pharmacokinetics and pharmacodynamics, they can also cause allergic responses. Over 100 approved biologics already list immune responses on their labels. As one example, a majority of patients taking Humira make ADAs (1). It often takes several months to a year for antibodies to build up and become a problem, but it is a key reason why patients on anti- TNF alpha inhibitors are often forced to switch medications.

The real problem arises when there is no alternative treatment. For instance, for patients with Pompe disease, there is only one approved enzyme: alglucosidase alfa. If patients develop ADAs to alglucosidase alfa – and the vast majority of patients do – the loss of alglucosidase alfa efficacy can prove to be fatal. ADAs also prevent a number of drugs from even reaching the market.

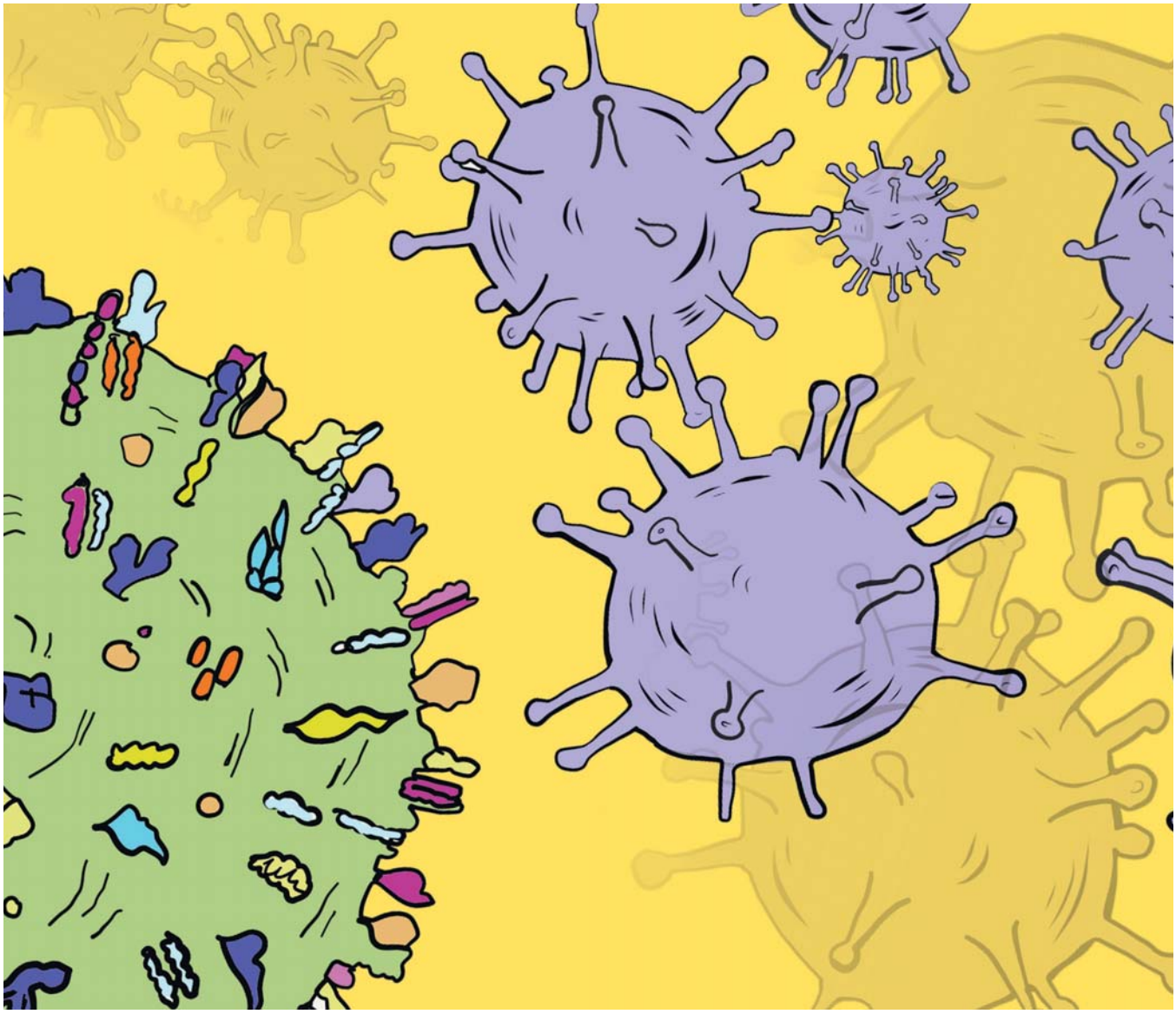
Antibody action

We need an approach to deal with ADAs that goes beyond "wait and see". At present, some physicians are avoiding certain approved medications because of the drug's immunogenic profile or are unaware that a patient has developed ADAs because they are not routinely monitored. Other physicians are experimenting with immunosuppressive cocktails to overwhelm the immune system to keep the ADAs at bay and allow the medication to work. However, the need to broadly immunosuppress patients comes with clear drawbacks and risks.

We have been aiming to improve the efficacy and safety of biologic medications by resolving the ADA issue. One of our cofounders, Ulrich von Andrian (the Mallinckrodt Professor of Immunopathology at Harvard Medical School) is one of the world's leading immunologists, and much of his work has focused on the role of dendritic immune cells. The dendritic cell acts as the teacher and sentinel of the immune system. They sample viruses and nanoparticles in general and, if they sense danger, they activate the immune system to respond by inducing the activation of virus-specific T cells and B cells, which leads to the production of specific antibodies to fight the danger. Von Adrian demonstrated that you can also achieve the opposite result by taking dendritic cells out of an animal and teaching them to induce immune tolerance to an antigen. He then reinjected those dendritic cells into another animal, which prevented the animal from making antibodies against the specific antigen.

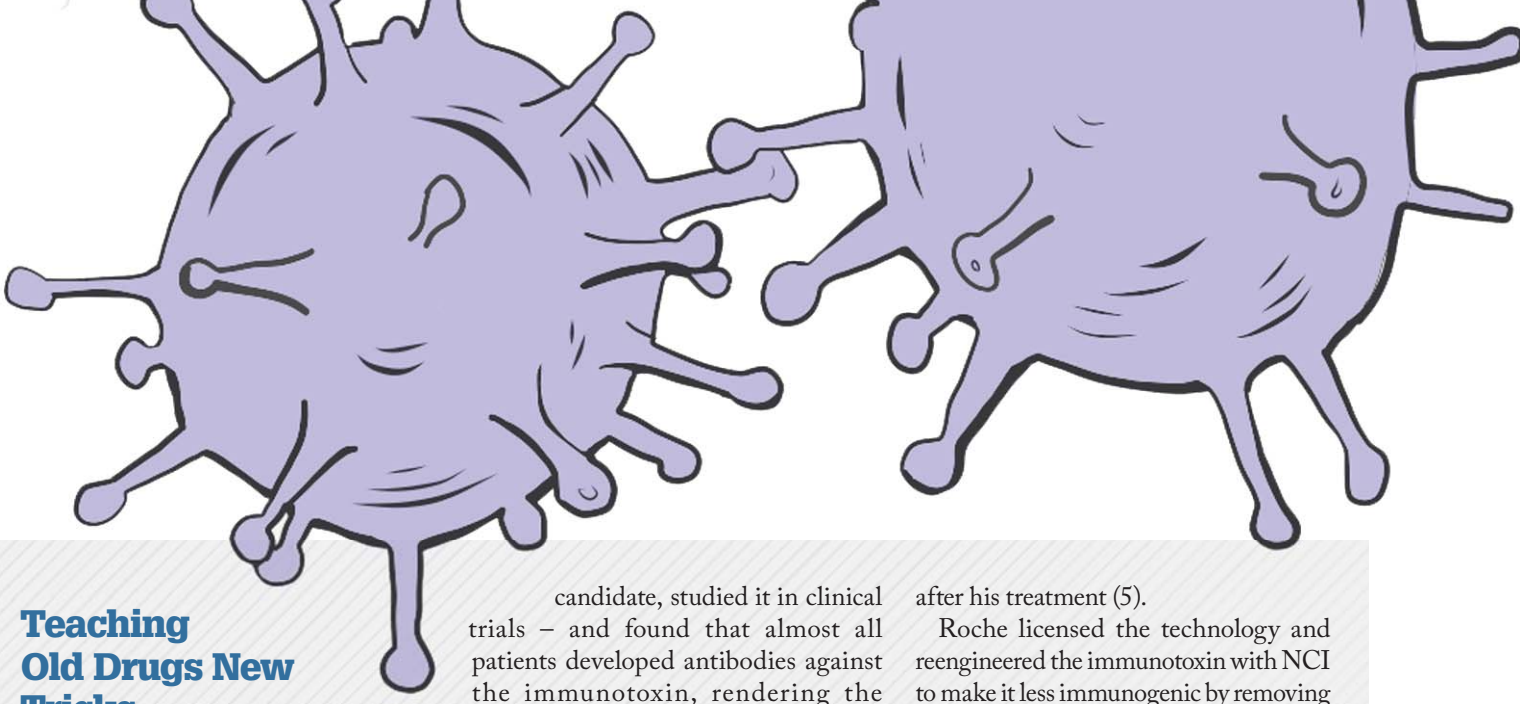
We believe that it is also possible to combat ADAs in vivo by using synthetic vaccine particles (SVPs). We have designed these nanoparticles with the goal of permitting them to "talk" to the immune system – telling it when to fight and, just as importantly, when

"The need to broadly immunosuppress patients comes with clear drawbacks and risks."



not to fight. We hope to use SVPs to program the immune system to elicit tolerance to a specific antigen, without impacting the rest of the immune system. Rather than taking the dendritic cells out of the patient and dosing them with a biologic and an immunomodulator in a petri dish to prevent ADAs, we enable the critical process – specifically SVP-Rapamycin dosed in combination with a biologic – to take place within the patient to induce longer term immune tolerance.

The design of SVP-Rapamycin took a significant time as we were looking to overcome serious scientific challenges and had to meet many important criteria. For instance, we wanted them to work when dosed both subcutaneously or intravenously. We wanted to ensure that these nanoparticles resembled viruses so that they would be taken up selectively by the dendritic cells. We designed the nanoparticles to remain intact once they were injected and to only release their payload once they were taken up by the dendritic cells. In addition, of course, we had to develop a means to produce the particles in a way that made business sense and could facilitate our scale-up. We have already translated our SVPs from in vitro, to mice and to non-human primates – and this research has been published (2).



Teaching Old Drugs New Tricks

Many promising treatments do not reach the market because of immunogenicity. As one example, Ira Pastan, a senior investigator with the US National Cancer Institute (NCI), discovered mesothelin, a protein that is overexpressed in mesothelioma, pancreatic cancer and other solid tumors. After identifying the target, Pastan started to work on recombinant immunotoxins consisting of an antibody fragment fused to a bacterial toxin payload intended to kill mesothelin-expressing tumor cells. NCI subsequently developed a product candidate, studied it in clinical trials – and found that almost all patients developed antibodies against the immunotoxin, rendering the drug useless.

NCI then opened a small new Phase I trial in which a small number of terminal patients with a rare form of cancer known as mesothelioma were dosed with the immunotoxin and a potent cocktail of immunosuppressant drugs. The results were compelling. While the vast majority of patients still formed ADAs and were forced off therapy, one patient was able to receive four treatment cycles and another was able to receive six treatment cycles. Both of these patients saw marked tumor regression, and one of these patients remains alive today more than five years after his treatment (5).

Roche licensed the technology and reengineered the immunotoxin with NCI to make it less immunogenic by removing certain epitopes, creating a product candidate known as LMB-100. Roche initiated a new clinical trial with LMB-100, but found that the compound was still highly immunogenic. Roche then returned the product and technology to NCI. In 2016, NCI and Selecta generated compelling preclinical data showing how SVP can prevent the formation of ADAs to LMB-100, which led Selecta to in-license the product candidate in 2017. Selecta and NCI are currently planning a Phase 1b clinical trial for this new combination product candidate, known as SEL-403.

But, of course, we needed to make the most important translational step of all – demonstrating that our approach would work in humans.

The right indication

In order to pursue our first commercial path for SVP-Rapamycin, we needed a suitable biologic candidate to showcase the potential of SVPs, and we had the following criteria:

- It had to be a product that we owned; we could have chosen to license out our technology, but we wanted to own the product for the first applications so that we would have full control of the development path and timeline.
- At the same time, we needed this to be a real commercial opportunity to address real unmet patient needs.
- We also wanted a product that would enable us to demonstrate a benefit very rapidly – both from an efficacy and from an ADA-mitigation aspect.
- In some cases, immunogenicity is built up immediately; flu shots are designed so that you only need one shot to have an immune reaction, and some biologic drugs provoke an equally strong response. With many other drugs, ADAs build up more slowly over the course of many months.
- We also wanted to find a medication that had clear biomarkers of efficacy as opposed to a longer-term clinical outcome.
- Lastly, we wanted to work with adult patients for our first indication. With hemophilia and other genetic diseases, the focus is often on treating young patients. However, as SVP is a new technology, starting with children would have erected high hurdles from regulatory agencies, parents and ethics committees.

Our screen led us to the chronic severe gout market. Gout is a very prevalent disease – there are around eight million patients in the US alone. It is caused by metabolites from proteins; specifically uric acid, which normally circulates in the blood at healthy levels below 6 mg/dL. Gout patients have an imbalance between how much uric acid is formed and how much is excreted through the kidney. If the concentration goes above 6.8 mg/dL, uric acid is no longer soluble, leading to the formation of crystals that can cause inflammation in joints and tissues. To get rid of the imbalance, you may need an enzyme called a uricase that targets uric acid. However, as the human body doesn't make uricase, it is viewed as foreign by the immune system, and ADAs form in the vast majority of patients (3).

We licensed one such enzyme, pegsiticase, and then combined it with our technology. By co-administering the enzyme drug with our SVP technology, we have generated data that show that we can prevent the formation of ADAs in human patients (4). I like to describe SVP-Rapamycin as a "negative vaccination." With a vaccination, you are sending a danger signal to the immune system to induce the formation of antibodies to fight an antigen. With SVP-Rapamycin, we seek to teach the immune system that the biologic is not dangerous and that ADAs should not be formed. We have already generated clinical data in support of the idea that SVP-Rapamycin that is administered with pegsiticase mitigates the formation of ADAs to pegsiticase. We are now in the middle of a phase II study and we have already started looking at the design of our phase III program, which we plan to begin soon.

Treat and retreat

Gene therapy could be a particularly promising area for SVP. Going back to hemophilia; what if we could teach a patient's liver cells to make the missing coagulation factor? Gene therapy would involve delivering genetic information encoding the coagulation factor into the liver cells, but to do that you need a vehicle, such as a viral vector. Of course, as these vectors are "viral," they are always immunogenic when you dose them systemically. Initially, the viral vector should induce liver cells to start making the missing protein. But, over time, expression may wane due to cell turnover in the liver. Currently, it is not possible to re-administer gene therapy because the immune system will have made ADAs after the first injection. This is a particularly challenging issue for pediatric patients, as cell turnover in the liver will be high as the children grow. As a result, systemic gene therapy dosing has been mostly limited to adult patients thus far. In preclinical studies; however, we have shown that by combining viral vectors with our SVP technology, ADAs can be prevented, making it possible to re-administer gene therapy.

"Currently, it is not possible to re-administer gene therapy because the immune system will have made ADAs after the first injection."

As the problem of ADAs becomes more understood, I expect to see greater regulatory oversight – and perhaps agencies in the US and other developed markets will begin to require companies to not only study immunogenicity during clinical trials, but also after a drug has been approved and is in regular use on the market. We urgently need to address this issue as the next generation of biologic therapies are developed. Particularly in the case of gene therapies, retreatment will be incredibly important for a number of inborn diseases for which no treatments exist today. If we want to progress medicine to the next level, we need to tackle ADAs. And I believe that the most effective way to do this is through antigen-specific immune tolerance.

Werner Cautreels is Chairman, President and CEO of Selecta Biosciences, Inc.

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Biosimilar Backer

Sitting Down With… Cyrus Krakaria, President of Biotechnology at Lupin Limited, Biotech Division, India.

You're passionate about the benefits of biosimilars – why?

There is no country on earth right now where medical systems are not under strain. Yes, biologics have revolutionized medicine by providing treatments for incurable diseases, but these medicines are expensive. However, it is possible to produce the same medicines at lower costs. And once the price point is adjusted, we can reduce the pressure on medical budgets. The money saved can be used for other (newer) life-saving drugs. Some people in the industry are against biosimilars, with some innovators scare mongering so that they can hang on to a monopoly, but we need biosimilars! Like it or not, biosimilars are an effective solution to healthcare costs – and will become universal as more governments start acting.

How did you get involved with the biosimilars industry?

I've worked in biotech for over 25 years. Much of my career was spent working for companies that produce biological entities, including Biogen, one of the oldest biotech companies around. I've had the good fortune to be involved in taking three biological drugs all the way from the clinic to commercialization, so I know the hard work that is involved. But at some point I began wondering about what comes next.

When I first heard about the concept of biosimilars, I must admit I was a little skeptical. I thought it would be very difficult – perhaps impossible – to copy a biologic considering that most biologics are made in natural systems. How do you engineer a different cell to produce the same biologic with the same post-translational modifications? I was intrigued and did more research – and I took it on as a challenge, because it would bring enormous benefits to patients. India-based Lupin has traditionally focused on generics, but biosimilars are a natural progression. Joining Lupin was a fascinating opportunity given that most of my career had been based in the US. And because India is relatively poor, many biopharmaceuticals are completely out of reach. What a difference it would make to be able to bring these essential medicines to a point where wider numbers of patients can afford them…

And actually, it isn't just a problem for countries like India. Think of the US; if someone is unlucky enough not to have insurance, then they are "written off." In a way, India is in a better position because biosimilars have really taken off so there is a lot of competition to bring prices right down.

Some people in industry have made comments about the safety of medicines made in India…

A significant percentage of all the world's generic medicines are made in India – patients all over the world benefit from medicines that come from India and I don't think a lot of people know how well these drugs have been made! All the major companies follow cGMP and the regulatory climate here is very effective for generics and biosimilars as regulators don't discriminate between innovator and copycat drugs – the final decision will be made based on quality. There are many misconceptions about the safety of biosimilars and manufacturing processes, but biosimilars tend to use newer manufacturing technologies than the innovator. I've seen head-to-head studies where the biosimilar drug could be better than the innovator drug because of the use of more modern technologies and high-end analytics.

Do you think biosimilars will ever take hold in the US?

Yes – eventually. Because someone somewhere is paying for the current system and that is not sustainable. I think uptake has been slow in the US because many of the innovator companies are based in the US, and they've had a huge influence on legislation. The hurdles for launching biosimilars in the US are significant. Even big pharma companies are struggling to launch biosimilars – forget about small companies like us! Things will remain difficult until there is an even playing field. Right now, contracts and rebates are preventing insurers from choosing biosimilars – so they aren't being used. And this does not incentivize the development of biosimilars, particularly for small companies. It is very expensive to get a biosimilar approved in the US, which means there is little leverage to reduce the cost of a biosimilar compared with an innovator product. Despite all of this, I am optimistic. It will change because things have to change. We have our eyes on the US market at Lupin. We have a pipeline of around 10 biologics and we want to take some of these to the global market. At some point we will crack the US market too.

How do you think the industry needs to change?

I would like to see a change in the way that biosimilar molecules are scrutinized and a simplification of the requirements for demonstrating biosimilarity. Science has improved a great deal – and will continue to improve in the future. We can clearly show whether a biosimilar has the same route or mechanism of action as an innovator drug – no matter how "dissimilar" it may be. And a lowering of regulatory hurdles does not mean we have to compromise safety and efficacy (which should never happen). It would be great to make it easier for biobetters to come to market. Right now a biosimilar must be similar, but it can't be better. If it's more potent than the originator then you'll need to spend more money on additional trials. But most companies cannot afford to do that. What a shame there is not more incentive to develop products that offer improvements for patients!

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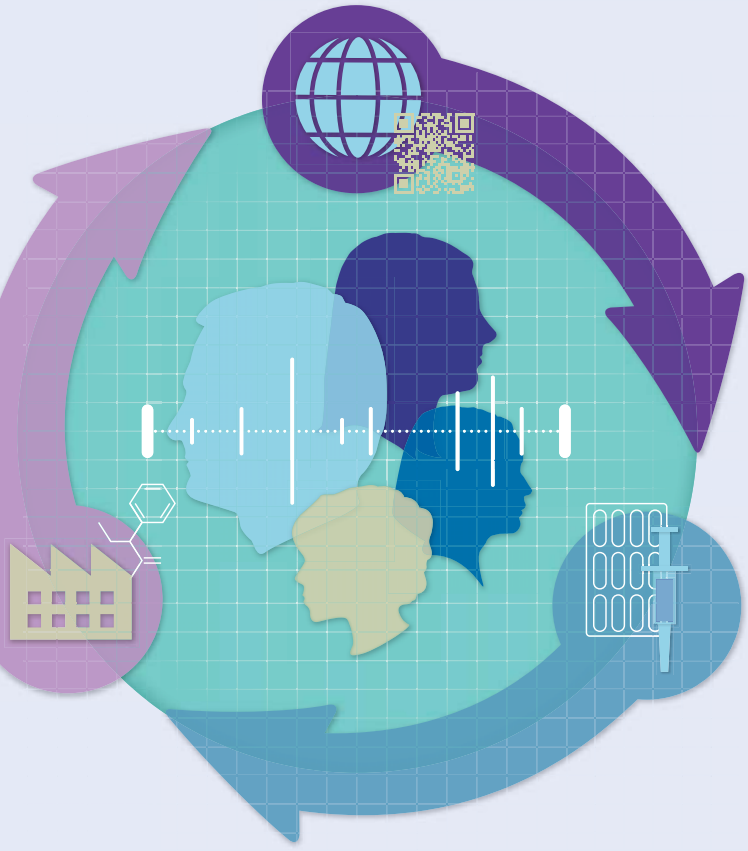

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