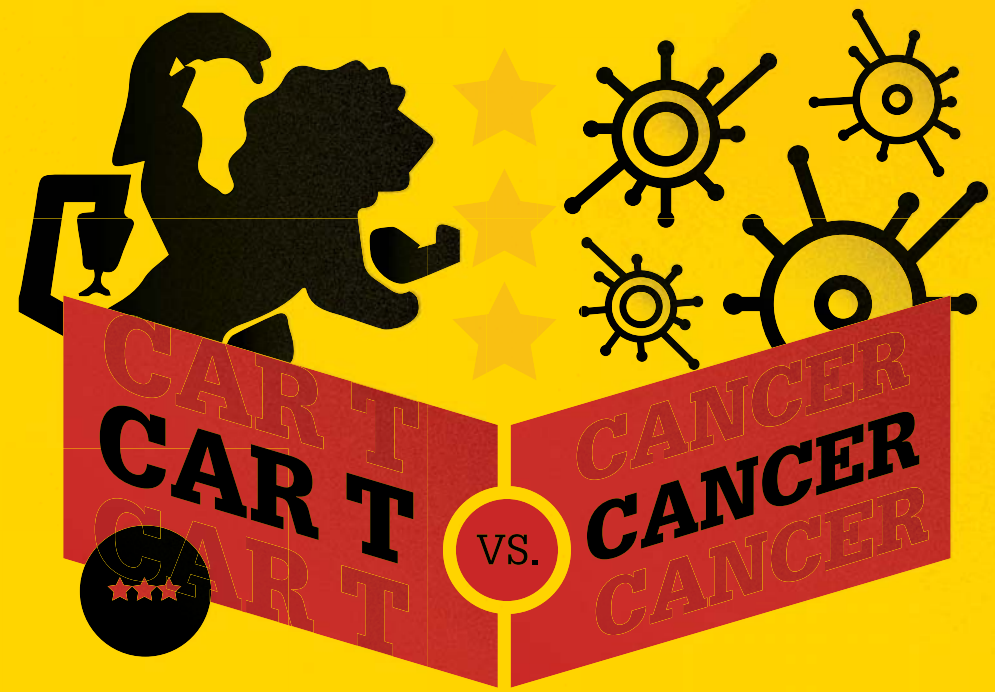
FEBRUARY 2020 # 62

the Medicine Maker™

THE WAR ON CANCER



18 – 29

A GAME-CHANGER **IN THE FIGHT** AGAINST CANCER

BUT WHAT DOES IT TAKE TO DEVELOP, SAFELY DELIVER **AND COMMERCIALIZE A CAR T?**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The Patient Is the Priority

As we announce a new Special Series of articles devoted to advanced medicine – and in light of public health crises and geopolitical changes – let's not lose sight of what's most important

The coronavirus is spreading. The UK has left the EU. In turbulent times, it can be easy to focus on the geopolitics or the "industry impact," but I wanted to briefly reflect on how individuals may be feeling.

At the time of writing, 1,016 people in China have died from coronavirus (2019-nCoV) infection, as well as one person in Hong Kong and another in the Philippines. The WHO has praised the Chinese government's response to the crisis but, amongst reports of censorship and police intimidation (1), others have questioned whether it was right to quarantine all residents of Wuhan with little time to buy food and medicine (2).

In Europe, although the Article 50 period is over, a great deal of uncertainty remains. How will the 67,000 people employed in the UK pharma industry be affected? And what about patients on both sides of the channel who rely on imported drugs? Even with "frictionless" trade, drug shortages are becoming increasingly common for parts of the UK (3). Much will depend on the decisions made by politicians, particularly in the UK, over the next 12 months (a scary thought for some). But while we're on the subject of British politicians, I'd like to offer some rare praise.

Partly through a number of Government-led incentives, including the Catapult network, the UK has used its strong research base to build the largest cell and gene therapy ecosystem outside of the USA (4). Politicians should be commended for recognizing and acting on the potential of advanced medicines.

But as with Brexit and the coronavirus, the focus should not be on geopolitics, but on the potential impact on individuals – on patients. The possibility of treating or even curing previously untreatable, life-threatening conditions with cell and gene therapies is enormous and incredibly exciting.

And that is why I am proud to announce a new Special Series of articles devoted to advanced medicine – starting this month with our feature with CAR T pioneers, Kite Pharma (on page 18). For the next four issues, we will devote a significant chunk of the magazine to cell and gene therapies; if you would like to contribute, please do get it in touch. Though manufacturing and logistical challenges will no doubt feature heavily, my hope is to keep the patients front and center in the discussion.

James Strachan
Deputy Editor

SPECIAL SERIES
Advanced Medicine

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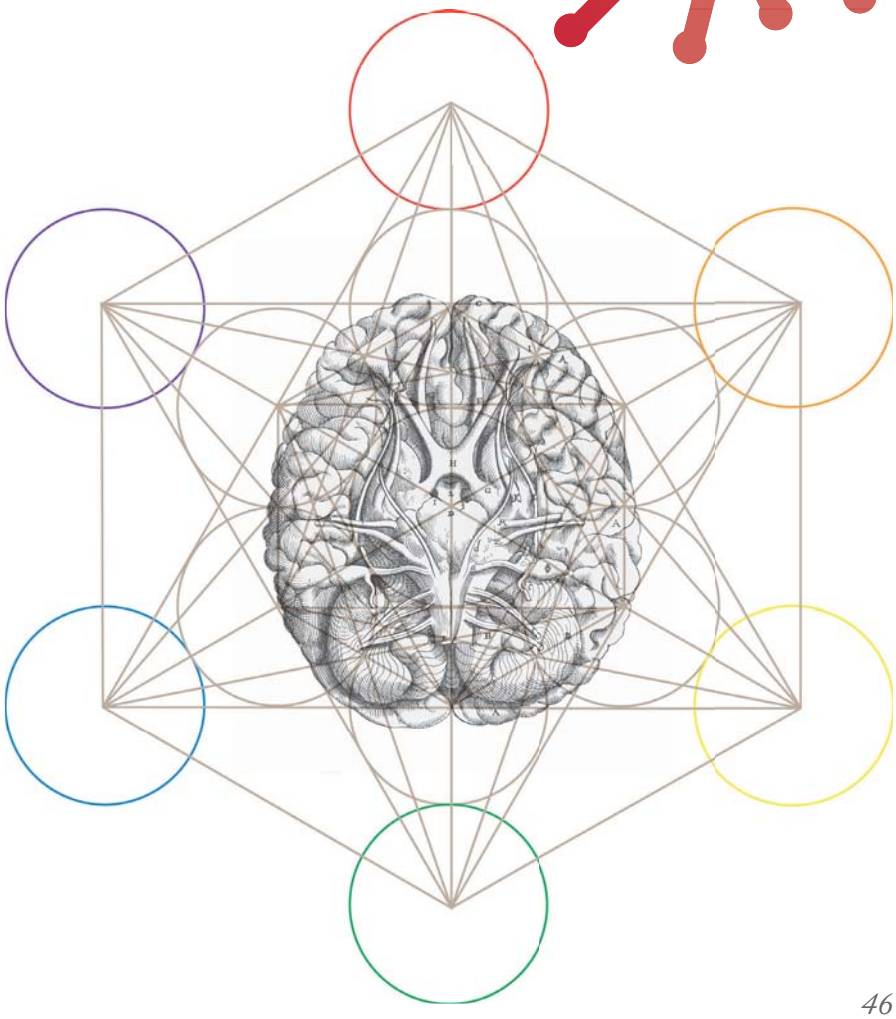

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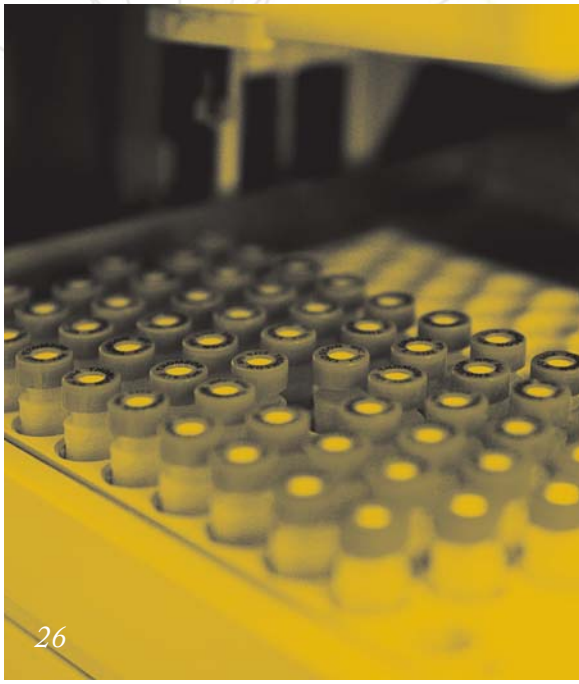

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Business

NextGen

Sitting Down With

the Medicine Maker

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SPECIAL SERIES
Advanced Medicine

Upfront

Research
Trends
Innovation

Meddling with Nature

The benefits and dangers of human germline genome editing

Human germline genome editing (hGGE) has great medical potential, especially in preventing heritable disorders; it can delete, add to, or even replace DNA sequences that are expressed in cells and passed onto the next generation. CRISPR-Cas9, the most widely used genome editing tool, targets specific DNA sequences and cuts them using the Cas9 enzyme, allowing for changes before the cell repairs the cut.

However, a new report from the UK Parliamentary Office of Science and Technology has urged caution, calling for a full review of the potential clinical effectiveness, cost-effectiveness, and risks and benefits of hGGE before deeming it safe (1). For those with serious monogenic disorders, such as cystic fibrosis, hGGE could ensure that their children won't suffer from the same condition. But for now, at least in the UK, the Human Fertilization and Embryology Act 1990 prohibits implanting embryos with altered germline DNA inside a woman. The Human Fertilization and Embryology Authority can award licenses for research – but only for projects that involve human embryos outside the body. Safety and ethical concerns have arisen around the world; in China, for example, one scientist claimed to have edited the genome of embryos that resulted in the birth of twin girls (2).

Before hGGE can be adopted in the clinic, a number of safety issues loom large. The main concerns involve edits being made at incorrect DNA sites, or potential unintended consequences of correct edits. There's also the possibility that a cell repairs cut DNA in an unanticipated way, or that the edited DNA sequence is absent in some cells. Genome editing techniques continue to improve – but the new report calls for further advancements before hGGE could be considered safe for clinical use.

With so many unanswered questions surrounding hGGE, some scientists want a moratorium on clinical heritable genome editing until a universal framework is established (3). Several international initiatives have already tried to address the issue – and, in 2019, the WHO launched a global registry for human genome editing that aims to track all research and make recommendations on appropriate legislation (4). Watch this space…

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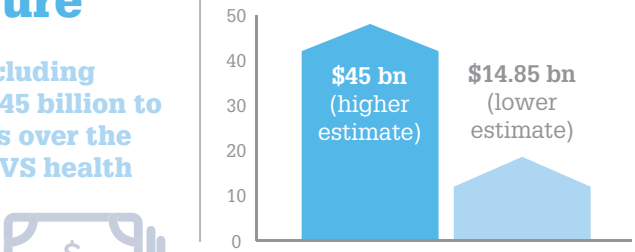
INFOGRAPHIC

Cost of a Cure

Gene therapies (including CAR T) could add $45 billion to US healthcare costs over the next five years, a CVS health report finds



Patients will be treated with

60% in vivo

40% ex vivo (e.g., CAR T)

ADVANCED MEDICINE IN BRIEF

The world's largest cell and gene CDMO, an exciting new TCR, and the global CAR T picture… We examine what's going on in advanced medicine

- Meet what some are calling the world's largest cell and gene CDMO. The new Center for Breakthrough Medicines facility will claim 680,000 square feet of the Discovery Labs complex, based in the King of Prussia area of Pennsylvania. Through $1.2 billion of funding by MLP Ventures, the new CDMO will employ 2,000 scientists, manufacturing experts, lab technicians, and support staff. The aim? To crack the production capacity problem.

- In a study that has received widespread media coverage, researchers used genome-wide CRISPR–Cas9 screening to uncover a TCR able to recognize and kill most human cancer types via the monomorphic MHC class I-related protein, MR1, while remaining inert to noncancerous cells. The new TCR was successful in mice and in vitro human cancer models.

- Citing Cancer Research Institute figures, a recent review offered insight into the global landscape of CAR T cell therapy. As of February 2018, there were 404 CAR Ts in the clinic, with the USA and China accounting for 80 percent of the total with 171 and 152, respectively. In terms of targets, both countries were focused on CD19 (over 40 percent), but in the USA, the second most common target of CAR T cell clinical trials is BCMA; meanwhile, Chinese researchers are tackling CD20, CD22, and GPC3.

Where's the Off Switch?!

Researchers seek a way to inactivate CAR T cells in case of adverse effects

As part of a Ludwig Cancer Research study, a team has devised a "STOP-CAR T" system that reversibly inactivates CAR T cells via small molecules. The approach is intended to dampen the effects of CAR T cell therapy when adverse reactions occur in patients. Although CAR T therapies have been praised for their success, they can sometimes elicit cytokine release syndrome. To build STOP-CAR T, the researchers attached the CD3-zeta activation domain to one molecule and the antigen-detecting portion to another. They also added to each chain the interacting domains of two unrelated proteins that spontaneously pair up inside the cell. This allows them to function as a single unit; however, the binding can be disrupted by systemically administered small molecules. So far, the system has only been tested in cell cultures and in mice.

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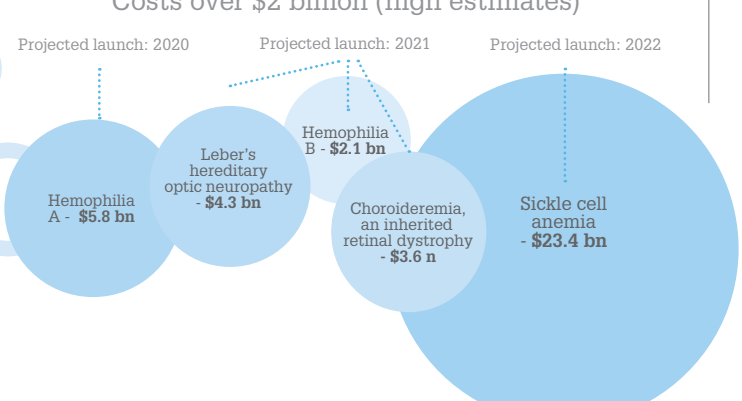

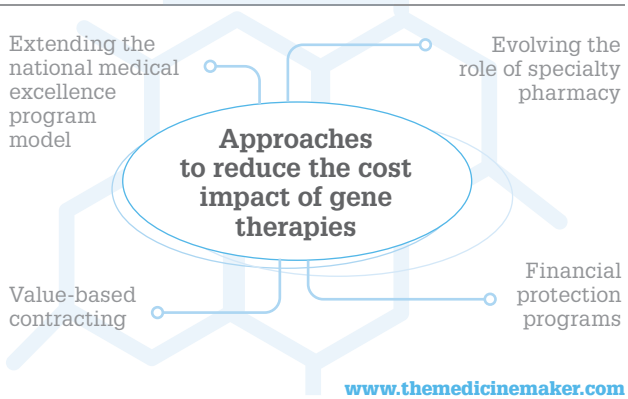

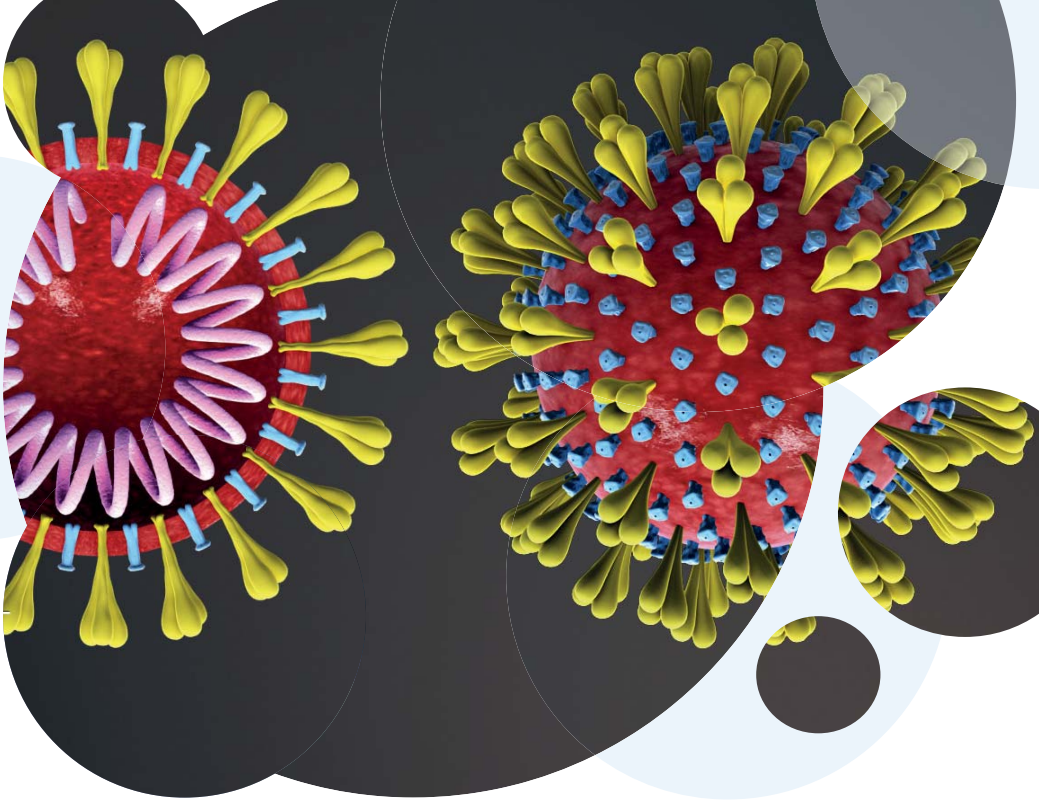

Coronavirus: To Action

Pharma companies get on board with vaccine and antiviral development activity to combat 2019-NCoV

Thousands of new cases of coronavirus are being confirmed every day. The novel strain responsible for the outbreak is 2019-NCoV, which was first detected in December 2019. Misinformation and panic have been rampant among the public, with the WHO being forced to step up and call out various myths on its social media platforms (no, sesame oil does not kill coronavirus – and neither does eating garlic).

The pharma industry is already on the case, searching for real treatments and vaccines.

Gilead Sciences, which has been working on a treatment for Ebola, is now collaborating with Chinese health authorities to see if the drug could help combat the symptoms of coronavirus. The drug, remdesivir, has reportedly demonstrated some success in treating SARS and MERS. A paper has also been published describing the use of the drug in a patient in the US suffering from 2019-NCoV (1).

Meanwhile, Inovio Pharmaceuticals is collaborating with Beijing Advaccine Biotechnology to advance development in China of INO-4800, a vaccine against 2019-nCov. Inovio says it has already commenced preclinical testing and preparations for clinical product manufacturing. The company will be leaning on Advaccine's expertise to run a phase I trial in China, in parallel with Inovio's clinical development efforts in the US.

Moderna is also looking to develop a vaccine, based on messenger RNA – and has received funding from the Coalition for Epidemic Preparedness Innovations (CEPI). The Vaccine Research Center of the National Institute of Allergy and Infectious Diseases, part of NIH, is working with the company on the design of the vaccine.

Johnson & Johnson will be focusing on both vaccines and antiviral therapies. The company will be taking advantage of its AdVac and PER.C6 technologies to upscale potential vaccine candidates – the same technologies were used to create an investigational Ebola vaccine, which is currently used in the Democratic Republic of Congo and Rwanda. The company will also be reviewing the pathophysiology of 2019-nCoV and examining whether previously tested medicines may have anti-viral activity.

Reference

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Peanuts for Thought

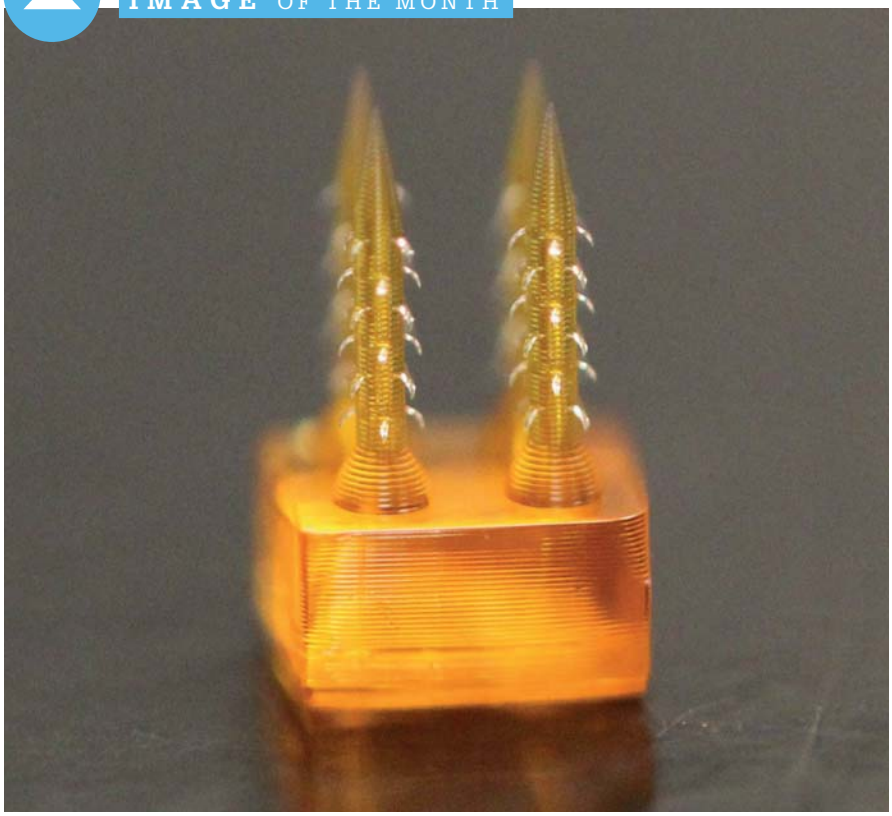
The FDA has approved the first treatment for peanut allergy

Palforzia (manufactured by Aimmune Therapeutics) – an immunotherapy made from peanuts – has been approved as a treatment for peanut allergy in children aged 4 to 17 years. And it's the first time the FDA has approved any pharmaceutical therapy for a food allergy.

Palforzia uses three phases of treatment: initial dose escalation, up-dosing, and maintenance. Over time, such treatment is able to mitigate allergic reactions to the allergen. Patients will still have to follow a peanut-free diet, but the treatment aims to help reduce adverse effects in the case of accidental exposure to peanuts.

Appropriately, the product has been designed with children in mind; for example, the maintenance treatment is formulated as a powder that can be mixed with a small amount of semi-solid food, such as apple sauce, yogurt, or pudding.

IMAGE OF THE MONTH



A Piercing Barb

Engineers from Rutgers used 4D printing to create tiny needles that mimic parasites with backward-facing barbs that the authors hope could replace hypodermic needles. Credit: Riddish Morde, University of Pisa, Italy

Would you like your photo featured in Image of the Month?
Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

Thank you, goodbye, and good riddance."

The EU's parting words to the UK – apparently, lost in translation (Croatia's EU ambassador mistook "good riddance" for "good luck"): https://bbc.in/2OCEm59

Point of Care, Point of Commercialization

UC Davis joins Orgenesis' point-of-care network to develop and commercialize cell and gene therapies in house

Orgenesis is building a network of hospitals around the world that are equipped to develop and process cell and gene therapies. UC Davis, USA, is the latest institution to get on board.

"The initial collaboration is focused on advancing the vector manufacturing process developed by UCD into a closed and automated system," says Peter Molloy, Executive Vice President at Orgenesis. "By automating the process in a closed system, Orgenesis will significantly reduce the associated costs as well as creating an agile and scalable solution, which is ideally suited for deployment throughout the Orgenesis POC network."

"We hope this collaboration is a first step towards a much deeper relationship where we work collaboratively with UCD to create a commercial pathway for many novel cell and gene therapies."

Rising to the ADC Challenge

The ADC market has continued to grow over the last decade – what advances should be embraced for true success?

The antibody drug conjugate (ADC) market has faced its fair share of disappointments. But as the industry gets to grips with the underlying chemistry, progress is being made – evidenced by the growing number of approved drugs. Here, Lisa L McDermott, Director of Process and Analytical Development at Merck, highlights the advances and technologies that will drive success in the ADC sector.

What are your predictions for the ADC market?

Though there have been advancements in the last decade, there are still many opportunities for further improvement for ADCs – particularly in the broader field of bioconjugation. As the field matures, I expect to see advances in three areas. First, cell targeting proteins will continue to improve in specificity

and companies will find ways to incorporate multiple modes of action into a single construct; second, payloads used will become more sophisticated and incorporate strategies for matching potency with delivery density; and third, linkers will continue to be better designed to play a major role in modification of the PK/PD profile of each construct.

We're all aware of how rapidly the field is evolving, so to keep up with changes in ADC development, manufacturing will receive more attention than ever before. We're definitely going to see production processes become more templated and process equipment more standardized. Coupled with this, I anticipate that process equipment and PAT systems will be designed specifically for ADC production and that we'll also see the widespread adoption of single-use systems for their well-documented safety and efficiency.

How will improved process understanding and automation help in ADC development?

During the discovery phase for an ADC project, structure activity relationships between the antibody, linker and payload are not fully understood. And that necessitates the production of libraries that can interrogate the chemical space and provide information for candidate selection. Automation plays an important part in providing these libraries by implementing parallel workflows that provide both material as well as data-rich information about each construct.

In the area of process development, gathering as much information as possible throughout the life cycle of a construct is very important. Due to the complex nature of an ADC, the technology used to monitor the process chemistry can be extensive. Tools are needed to understand both large and small molecule chemistry. Unlike more traditional areas of chemistry, fewer at-scale batches are produced for ADCs, but continuous monitoring can provide trending information and quickly identify any risks to controlling the process.

Will the market evolve fast enough to make way for ADCs?

I believe the market will directly respond to our ability to develop effective and safe products, and I don't think it will stop with ADCs. The technical community continues to develop bioconjugation techniques that use targeted delivery mechanisms to provide the patient with effective treatments with less off-target effects, lower total dose, and improved quality of life

In My View

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

Why Do We Keep Failing?

With so much time and money invested into pre-clinical research and early phase clinical trials, why are compounds still failing at the final hurdle?

By Adrian Wildfire, Scientific Director at SGS Life Sciences

It was Thomas Huxley who wrote, "The great tragedy of science [is] the slaying of a beautiful hypothesis by an ugly fact." Pharma's recent history is filled with examples where unexpected proofs regarding lack of efficacy have emerged to kill promising products late on in their development cycle.

Late-stage candidate failure can heavily impact a company's stock and projected earnings. One of the best-known examples in recent years is Novavax's ResVax. ResVax is a respiratory syncytial virus (RSV) vaccine targeting the post-fusion F-protein. Despite promising results at phase 2, late-stage trials failed to meet their primary endpoints. Subsequently, Novavax's share price fell by 96 percent over a five-year period.

In another example, a lack of efficacy observed for Regeneron's anti-RSV antibody suptavumab led to losses of over $270 million in 2017. This humanized-monoclonal, also failed to meet its primary endpoints at phase 3, despite being the subject of "accelerated development" aligned to encouraging early phase data. In the same year, Aviragen's BTA585 drug failed show significant reductions in viral load in a controlled human infection trial. This additional reverse brought total financial losses in RSV therapy investments alone for just one year to over $1 billion, inclusive of share price adjustments.

The industry recognizes that the cost, as measured both in time and money, of bringing a drug to market is increasing – currently, estimates are in the region of $2 billion, spread over a period of up to 12 years (based on a final success rate of approximately 10 percent). Given the enormous sums involved, why do so many drugs fail so late in the process? Prior to 2000, the main reason for candidate failure in late phase studies was safety. Improvements in PK/PD modelling reversed this trend, but other variables emerged to fill the gap. Efficacy has now leap-frogged safety to become the primary reason for late-phase failure, with commercial pressures such as price or pipeline rationalization also contributing significantly to withdrawals or late-stage project termination.

Given the structure and principles of drug development, a lack of proven efficacy should be a minority reason

"Given the enormous sums involved, why do so many drugs fail so late in the process? Prior to 2000, the main reason for candidate failure in late phase studies was safety."

for failure. Prognostic correlates (for example, correlates of protection) and other objective measures should be evidenced during pre-clinical and early clinical studies, primarily during phase II, before a product progresses to a large field trial. Allied to the value or strength of prognostic markers, relevant powering (which is to say, recruitment of subjects to achieve "n", the number required to demonstrate that observed events are unlikely to be related to the product's effects and not to chance), is essential if outcomes are to be considered valid. Study centers with a track record of success are historically more likely to meet enrolment targets – often because they have proven recruitment strategies (for example, rare-disease databases, investigator engagement and, most importantly, enthusiasm). These, in addition to such measures as time from ethics approval to first enrolment and the allocation of a dedicated clinical trial coordinator, all make for good predictors of success or failure to enrol. Adequate funding of all of the above may also impact significantly on success rates, with around 22 percent of small/medium companies being unable to conclude trials for financial reasons alone.

The norm for return on investment (ROI) for pharma is 25 percent or less, based on drugs already well into the clinical development cycle. Many of the reasons for poor ROI remain intractable, such as candidate failure due to low incidence of disease and undesirable side effects (adverse events). Late-stage findings regarding lack of efficacy remain irregular as the discovery process is predicated on finding effective ways of altering actions and reactions in a predictable manner for a given set of indices. Where such indices or endpoints are intractable (e.g., symptom resolution in hospitalised patients) or poorly prognostic, trials have a greatly increased chance of failure.

Candidate failures will never be wholly avoidable, as research by its very nature incorporates elements of the unknown, but there are steps that can be taken early in the research cycle to reduce the number of late stage failures. Some of the issues with efficacy could perhaps be resolved by better interpretation of pre-clinical data and less optimistic analysis and interpretation of data. One factor above all others that has been proven to safeguard and accelerate development is the availability of a strong correlate of efficacy. Many studies must rely on observational or subjective measurements, such as symptoms, to infer that a treatment improves a patient's condition or welfare – often due to the lack of objective markers of disease. Strong correlates can considerably shorten the time to licensure for drugs and vaccines but, equally, the incorrect use or interpretation of correlates can confuse rather than clarify the response of an individual to a given intervention. For example, random, ordinal rankings of disease severity, such as "1-25", "A to D," "mild to severe" may be poorly transferrable or comparable between studies. Correlates may, upon investigation, fail to show correlation to effect, being non-functional covariates with little or no direct relation to mechanisms of interest. We should, therefore, be careful in the invocation of correlates to prove or disprove cause and effect. It's also worth noting that out of over 150,000 published biomarkers in 2011, only some 100 are regularly used in clinics today.

"Many studies must rely on observational or subjective measurements, such as symptoms, to infer that a treatment improves a patient's condition or welfare – often due to the lack of objective markers of disease."

To estimate the real-world predictive value of healthy volunteer studies, we often have to look backwards; using data from similar late phase studies and the prognostic value of animal and early clinical efficacy data in that indication. Additional in silico or in vivo prognostic modelling prior to testing novel compounds in large field studies may also decrease risk. Increasingly, in my own view and those of many clinical trials professionals, controlled human infection modelling (CHIM) can add value as the "next-step" from preclinical work in animals and provide strong bridging data to humans. Employing the correct human model to substantiate pre-clinical findings can validate decisions regarding both candidate selection and dose selection. Recent studies that I have been involved with have seen the CHIM model provide solid evidence of efficacy and offer additional immunological data to assist in vaccine design and delivery programs.

Getting pivotal phase II studies to be predictive of field behavior is the key to safeguarding investment in phase III. There is no crystal ball to reliably predict low-incidence safety signals, but efficacy should be a given by the time the sponsor invests large sums into a large field trial.

Greater Transparency, Fewer Shortages

Greater transparency in supply chains will help address shortages

By Dawn MacNeill, Head of Supply Robustness, Process Solutions, Merck

In 2011, the number of new drug shortages in the US spiked at 267, but the regulatory response was thorough and prompt, including the 2012 FDA Safety and Innovation Act and the 2013 Drug Supply Chain Security Act. Industry consortiums also leapt into action. To name a few initiatives, the Parenteral Drug Association (PDA) established preventive end-to-end controls for drug shortage risks based on criticality of the drug product, patient impact, and overall product risk evaluation. And Xavier University published Good Supply Practices for the 21st Century.

But after three years of relative stability in the US, the number of new drug shortages rose to 186 in the year 2018; the highest number since 2012 and up 26 percent from 2017. There are a number of complex dynamics and market forces implicated in drug shortages, and the issue is amplified by rapid pipeline growth and the push for geographic expansion. The same factors are leading to increased investments in global biopharmaceutical manufacturing capacity. Growth and expansion results in an increase in the length, depth and breadth of supply chains, which in turn, increases their vulnerability to disruptions.

A major contributing factor to drug shortages is the availability of raw materials. Though it can be difficult to pinpoint the exact culprits captured in this broad category, issues with raw material supply and quality can most certainly jeopardize the consistent manufacture of drugs. In addition to regulatory initiatives and the efforts of industry organizations, suppliers to biopharmaceutical manufacturers must become active participants themselves in mitigating the risk of supply disruptions and enhancing process predictability and control. But they can only do this if biopharmaceutical manufacturers and regulatory authorities engage with them. For example, biopharmaceutical manufacturers should share basic information with suppliers about the chemicals and consumables specified in their manufacturing processes, their batch requirements, and their production schedules. If these bill-of-materials are used to manufacture a drug on the World Health Organization List of Essential Medicines or a drug for childhood cancer, the chemicals and consumables could be deemed critical by the supplier and result in more robust risk mitigation. Such information could influence suppliers' supply chain activities, such as forecasting, capacity planning, safety stock inventory planning and dual-sourcing, as well as allocation activities in the unfortunate event of capacity constraints.

"After three years of relative stability in the US, the number of new drug shortages rose to 186 in the year 2018; the highest number since 2012 and up 26 percent from 2017."

Similarly, sharing information related to critical process parameters and unit operation results could lead to an improvement in quality control and a reduction in raw material variability – contributing to enhanced process characterization and control, and a more mature quality management system. Ultimately, this could support biopharmaceutical manufacturers in their pursuit of a competitive quality rating.

Even one drug shortage is too many for the patient who suffers the most. Though it is unlikely that we could achieve the goal of zero drug shortages, biopharma manufacturers could realize better success if they collaborated more with their key suppliers. Greater transparency and trust in partnerships is a must to develop more robust supply chains.

News Flash

Biotage® Selekt has arrived

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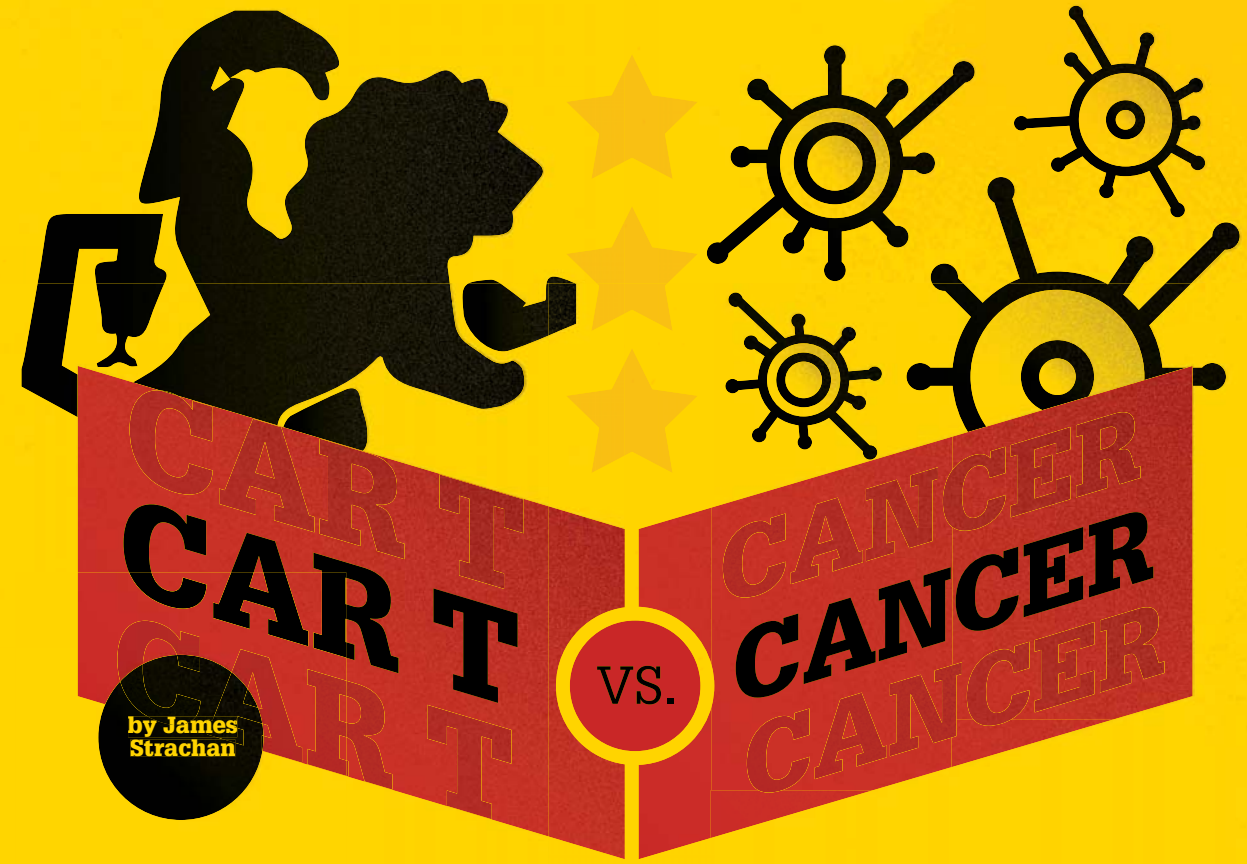


by James Strachan

the Medicine Maker *Presents*

A **GAME-CHANGER** IN THE FIGHT AGAINST CANCER, BUT WHAT DOES IT TAKE TO DEVELOP, SAFELY DELIVER **AND COMMERCIALIZE** A CAR T?

JOHN ROSSI
DIRECTOR OF TRANSLATIONAL SCIENCES, KITE PHARMA

BETHANY DUDEK
EXECUTIVE DIRECTOR, QUALITY HEAD EUROPE, KITE PHARMA

DICK SUNDH
HEAD OF EUROPE, KITE PHARMA

Chimera by Studio Fibonacci from the Noun Project

DRIVING CAR T CELL THERAPY

John Rossi, Director of Translational Sciences at Kite Pharma (a subsidiary of Gilead Sciences), talks about the bright future of CAR T cell therapy – and the life-changing implications for cancer patients

HOW DID YOU FIND YOUR WAY INTO CAR T CELL THERAPY?

I joined Amgen in 2002, supporting a range of biomarker development programs spanning inflammation, metabolic disorders, oncology, and more.

In 2015, I came to Kite, where I focused on developing a translational strategy to support the development of Yescarta (axicabtagene ciloleucel, a CD-19 CAR T cell immunotherapy). My initial experience at Amgen allowed me to blossom into a translational role at this much smaller company, where I am now a Director in the Translational Medicine Group.

WHAT IS THE TRANSLATIONAL MEDICINE GROUP?

What we do – everything from clinical pharmacology to correlative analysis – would traditionally be covered by multiple teams in a larger pharma company. Having intimate knowledge across many areas has allowed us to support the key functions within the Cell Therapy Division, and we work very closely with many different parts of the organization. Currently, we are characterizing the mechanisms of resistance, relapse, and toxicity so that we can better manage our patients.

Our multifunctional team is really a legacy of where we started: a small start-up company that required each of us to wear many hats. As the company grew, the Translational Group continued to manage these responsibilities. The initial model has been maintained through time. And we're proud of that.

WHAT ARE THE DRAWBACKS OF THE CURRENT GENERATION OF CAR T CELLS?

The most recent data show that 40 percent of our patients are in remission after two years, and the overall response rate is 80 percent. The next generation of products will serve the 30 percent or so of patients who relapse due to losing their targeted antigen. I don't think we are able to talk about a cure yet, but that is the ultimate goal.

Neurologic toxicity is a big issue that we need to figure out and control. About a third of patients experience notable neurologic events. These are currently managed with corticosteroids, but a greater mechanistic understanding will allow more targeted interventions.

WHAT ARE THE MAIN CHALLENGES IN DEVELOPING NEW CELL THERAPIES?

Any expression of a target on normal tissue allows CAR T cells to cause damage. We need to identify better non-essential targets, a task that has proven to be a huge challenge to the field. An alternative is currently being investigated: using engineered T cell receptors to target an HLA-presented peptide restricted to the tumor.

The next challenge is to overcome barriers in the tumor micro-environment. We hope to engineer the next generation of cell therapy products to counter checkpoints, myeloid-derived suppressor cells, and regulatory T cells.

Kite has a trial program, in partnership with the National Cancer Institute (NCI), to further identify and develop unique T cell receptors. We use strategies such as synNotch – synthetic biology based on a logic system that requires two antigens to activate the T cell. The cells would also be engineered to express tethered IL-15 to bring a cytokine that would promote proliferation of that T-cell product within the tumor microenvironment.

We are also thinking about partnering with Gilead to use different molecules to reprogram the tumor microenvironment so that is more permissive to T cells.

HOW FAR AWAY ARE WE FROM THE NEXT GENERATION OF THERAPIES BECOMING REALITY FOR PATIENTS?

In oncology, we should see some of the combination studies within the next three years, and cell engineering after that. We are close, but it takes time to really figure out how to maintain the added functions without losing the T cell's ability for cell killing. We may be able to see the successes of these futuristic, next-generation products sooner if we invest properly and pick the right targets and approaches.

We have come from single-center trials treating 10 to 20 patients and now treat thousands of patients both in the US and Europe. We continue to learn, accelerating the development process.

Additionally, cell and gene therapies are going to continue to improve and advance different medical conditions such as thalassemia and other blood disorders. We will soon see cell therapies for immune disorders. The future is very bright for all areas of engineered T cell therapy.

"Our work is *transformative*. Cancer patients who were given *three to six months* to live are now back with **their families**, *back at work*, and have healthy, **normal lives.**"

WHERE WILL ONCOLOGY TREATMENT BE IN 20 YEARS' TIME?

I believe in my heart of hearts that we are going to use off-the-shelf progenitor stem cells engineered to target cancer cells and overcome the tumor microenvironment. Off-the-shelf therapies will reduce costs and increase access to a great number of patients. It will take time, but it's where we are headed – Kite has an active program in that area.

It is also crucial that we continue to invest in academic science that seeks further advances. Kite is sponsoring numerous studies, providing funding and samples to some of the best and brightest in the field. We hope that governments around the world will continue to invest in basic research that is ultimately going to drive these next generation therapies.

CAN YOU GIVE AN OVERVIEW OF SOME OF YOUR MOST RECENT RESEARCH?

We have been investigating pre-existing inflammation within the tumor microenvironment and how that relates to critical outcomes for CAR T cell therapy; those patients with less widespread disease and whose tumors have a pre-existing cytotoxic infiltrate ("hot" tumors) tend to have a better response rate. And that tells us that earlier lines of CAR T cell therapy may increase the overall response rates and reliability, and we should consider strategies to convert a "cold" tumor to a "hot" tumor.

We have also been looking at vector integration sites using the retrovirus from CAR T cell therapy manufacturing. The goal of the study was not only to characterize the integration site, but to convince ourselves – and the regulatory agencies – that the virus provides a low risk for secondary malignancy in patients. We found that the integration sites are highly variable across patients. But importantly, there weren't any clones that particularly expanded out during manufacturing. A competitive growth advantage could have led the clone to transform into a T cell leukemia layer, for example. This is nothing new, and is consistent with the literature. But this is a significant study, as it characterizes the integration patterns and safety profile of the retroviruses used to manufacture our T cell. And it should help to lift the fear of gene editing.

TO WHAT EXTENT SHOULD CELL AND GENE THERAPIES BE COMBINED IN ONE FIELD?

Gene and cell therapy approaches are intertwined. Cell therapy without any genetic engineering has shown some success, but gene editing will continue to be heavily used to advance cell therapy. Next-generation products are really going to rely on gene therapy approaches to make a T cell product highly effective across a number of different cancer indications.

WHAT KEY LESSONS WILL INFORM FUTURE TREATMENTS?

The first lesson is critical: developing a robust, easy, streamlined manufacturing process that consistently produces an efficacious product. It's hard to scale up! The process we have developed for anti-cellular CAR T cell therapy consistently yields a product, with a relatively quick turnaround time of 17 days – critical for very sick patients. Manufacturing prowess and know-how are at the core of autologous cell therapy, as the technology currently stands.

The second lesson was not an easy one. A multiple myeloma program was terminated early because we didn't feel that our product was better than the products already in clinical trials. We learned that it is in no way trivial to develop a next-generation product to beat the success that we have with current CD-19 CAR T cells (which had been development for about 30 years prior to approval).

Kite's next product will benefit from both these lessons. We know what works and also what doesn't work, and we will continue to build on that.

HOW IS KITE'S WORK BENEFITING PATIENTS?

Our work is transformative. Cancer patients who were given three to six months to live are now back with their families, back at work, and have healthy, normal lives. Even patients who relapse are able to have more time with their families.

There is still progress to be made. Cancer is a tough beast, but this generation of CAR T cell therapies are helping people across the US and Europe, and hopefully soon the rest of the world.

★★★

CAR T CELL THERAPY: REDEFINING QUALITY

★★★

With CAR T cell therapy, quality takes on a whole new meaning. Bethany Dudek, Executive Director, Quality Head Europe at Kite, walks us through the challenges involved in ensuring CAR T cell therapies are delivered to patients safely and as quickly as possible.

With Bethany Dudek

I have worked in quality for both traditional biotech and pharma companies (as well as in manufacturing and technology transfer), and I've found that there is often a disconnect between what quality does and what the other departments do – they're seen as very separate parts of the business. With CAR T cell therapy, everything is connected and the role is much broader. For example, at Kite, I am responsible for all aspects of quality for the cell therapy products that we supply in Europe. My role spans QC release, qualifying the infusion centers that administer the product, various aspects of building the new manufacturing plant, various records and documents, as well as oversight of the distribution networks. This presents many challenges. When thinking about the quality journey of a CAR T cell therapy, the first and most obvious challenge is that each batch is

"I've found that *there is often* a **disconnect** between what *quality does* and what the other **departments** do – they're seen as very *separate parts* of the **business.**"

autologous (specific to each patient). This means ensuring that the chain of custody is watertight from the moment the product leaves the patient to the moment it is reintroduced to the patient.

Digitalization of this supply chain information can be a significant help from a quality perspective. We've created a patient portal for our products, which we use to track patient material and interface with our customers. This gives us oversight of the whole process. We understand how the chain links together and have identified key performance indicators that we check to ensure everything is happening as it should be along the supply chain. We also use qualified vendors to transport products from our approved hospitals to the manufacturing site. The infusion centers know how to receive the product, how to confirm that it has been shipped without issue and that they can receive it safely and prepare the patient for administration of our product. All of this is integrated into the patient portal, which interfaces with our internal IT system, allowing us to track everything along the way and react to anything unexpected.

This is a world away from the traditional scale-up manufacturing model, where you manufacture to an inventory target. There, if you need more product, you simply add more and larger bioreactors and columns. And from a quality point of view, consistency and characterization is the name of the game – with everything you're working with. With a CAR T cell therapy, your product is inherently variable and you must build that into your quality systems to the best of your ability.

Another thorny issue is testing: the methods we use are very complex. These aren't the typical tests seen in a traditional pharmaceutical manufacturing facility. Only highly trained staff are able to carry out those methods – and such people are in high demand (as was discussed in The Medicine Maker's December feature with ISCT) (1). At Kite, we spend a lot of time training staff and ensuring a deep understanding of the scientific reasons behind testing in a certain way.

Testing and other ATMP requirements are quite similar in the US and EU. There are, of course, some nuances, but overall they are aligned on a lot of the concepts and messaging. Within Europe, things can be a little more challenging because individual countries have their own local requirements or specific questions regarding CAR T cell therapy. This has a lot to do with the knowledge base within a country and whether there are already cell and gene therapies available. We work closely with our local affiliates to address any issues.

NEED FOR SPEED

Speed is the name of the game when it comes to CAR T cell therapy manufacturing. As Dick Sundh says on page 26, we're often treating patients that only have weeks to live and every day counts. Here, quality is integral to timelines and we work very closely with manufacturing to schedule our activities around theirs – down to the hour. As soon as we harvest cells and formulate our final product, we immediately start all of our QC testing. Once a sample is being

> "Often in quality, people *will go to you* as the expert, **but** we're *always learning* in this sector – **new situations**, problems and *ideas* arise all the time and you have to be **willing to learn.**"

tested in the QC lab we know exactly when they're going to finish and give us the result. As soon as the results come in and we confirm everything is correct, we immediately release the batch and communicate that it is ready for shipment to location.

We've had to really drive for innovation in our processes to ensure that we can identify problems and solve them quickly. The speed at which we are now able to get through all the documentation, while meeting the regulatory (ATMP) requirements has been quite amazing. Indeed, I have learned a lot as well!

But there is scope to further reduce turnaround times in the future. This would be possible through the development of shorter assay times. One of the longest assays we have is sterility testing, which is a seven-day test. Traditionally, that would be a 14-day test, but new technology has become available in response to the demand for shorter assay times in cell therapy manufacturing. We're always on the lookout for new innovations and there's huge potential for technology to streamline quality and manufacturing process further.

What we see in advanced therapies is that there is a significant business drive to reduce turnaround times and quality processes. I expect to see some of the more innovative approaches we take to quality in the ATMP sector eventually trickle back into traditional pharma.

RAISING THE STAKES

As I mentioned earlier, often people will see quality as a separate organization that always slows things down, but our goal is the same as everyone else's: we want to get the product to the patient as quickly as possible while ensuring safety. My approach is to think about how, as an organization, we can navigate the regulatory quality requirements in the most efficient way possible. It's a solution-orientated approach, and we do our best to foster a collaborative environment with many perspectives to combat problems when they arise.

And for CAR T cell therapies in particular, it's important that everyone in quality spends time in the manufacturing plant to understand the product they are working with and how it is made. This is especially so because in certain jurisdictions, we are permitted by the regulators to, in some circumstances, release a product out of specification. This speaks to the uniqueness and potential benefits of these products to patients, where the balance of risk to reward in these therapies is different when compared to traditional therapies. But that means, as someone in quality, you have to fully understand your therapy and what its potential impact may be. Often in quality, people will go to you as the expert, but we're always learning in this sector – new situations, problems and ideas arise all the time and you have to be willing to learn. And you have to take all of the experience and learnings you've had throughout your quality career and apply them in new ways for cell and gene therapy.

Bethany Dudek is Executive Director, Quality Head Europe, Kite, USA

Reference

1. *B Levine, "Stirring the Talent Pool" (2019). Available at: https://bit.ly/31v2uvv*

HOW TO **COMMERCIALIZE A** CAR T CELL THERAPY

Dick Sundh is Head of Europe at Kite, a role which includes responsibility for negotiating reimbursement (using often new and innovative payment plans) with payers across the continent. He explains what it takes to commercialize CAR T cell therapy.

WHAT ARE THE MAIN CHALLENGES OF NEGOTIATING A REIMBURSEMENT SCHEME FOR A CAR T CELL THERAPY?

For many countries, cell and gene therapies – especially CAR T cell therapies – are completely new and payers are working things out for the first time, but they invariably recognize the potential benefit these therapies bring to patients. This is why we achieved reimbursement in Europe within one-and-a-half years, which is relatively quick in oncology, never mind for a complicated and brand new therapy area.

Innovative reimbursement schemes where discounts are applied when the therapy doesn't have the intended effect have proved successful in working towards getting our therapy reimbursed. But we found that many countries are

> "We're not talking *about delivering* an **off-the-shelf** therapy. From *manufacturing*, to **commercial**, to clinical, everything is brand new *and* we're only **figuring things out** as we go."

unfamiliar and do not have procedures in place to implement new payment plans. That isn't to say they aren't keen, but it's the realities of implementation that can be tricky. This is why CAR T cell therapy is a team sport. Our job in the commercialization team isn't just to explain the benefits of our therapy - it also involves working collaboratively with payers to help them accommodate new payment models.

My proudest moments at Kite have come when we finally treat a patient in a new market for the first time. It's incredibly difficult to bring these therapies to a new market but we're proving it can be done!

MUCH OF WHAT KITE IS DOING IS COMPLETELY NEW...

It is. Not only with payers but across the board. We're not talking about delivering an off-the-shelf therapy. From manufacturing, to commercial, to clinical, everything is brand new and we're only figuring things out as we go. We find that communication and collaboration – both internally and externally – is crucial to what we do. Externally, we work very closely with our network of hospitals so that we can ensure that there is an apheresis centre able to deliver the CAR T cell therapy safely, effectively and within tight deadlines.

Internally, we have created a culture of patient centricity and one of close collaboration. When you're doing something so new you have to learn from your challenges and share those learnings effectively.

HOW IMPORTANT ARE TIMELINES FOR CAR T CELL THERAPY?

Absolutely crucial. Often, the average lifespan for the patients prior to treatment is six months. And for some patients, they may only have weeks to live if they can't get access to CAR T cell

"Looking ahead, *we will* find ways of **automating autologous** cell therapy manufacturing and *improving* the time it takes to **qualify** and deliver these therapies."

therapy treatment. There's a chance that reducing turnaround times by even a single day could be life-changing for a patient and that is why it is central to all we do. You have to constantly innovate to figure out ways of reducing timelines; for example: how to speed up processes for qualifying new apheresis centers? How can we streamline the process for booking patients at the apheresis center? How can we reduce the amount of manual interventions in the process, which require strict oversight, through automation?

FROM A EUROPEAN PERSPECTIVE, WAS THIS A FACTOR IN YOUR DECISION TO BUILD THE NEW MANUFACTURING CENTER IN AMSTERDAM?

Indeed. There are a number of factors that impact the speed at which you can turn around a CAR T cell therapy. Manufacturing and quality are obviously key, but so too is logistics – and the location of your manufacturing center is a key component of that. The first point is that we're much closer to patients in Europe – we do not have to ship to another continent and back to treat and reintroduce the cells. It is also very difficult to find a spot five-to-10 minute drive from an airport with direct flights to major European cities. In fact, Amsterdam is one of, if not the only, place where we could do that. We also have a research facility in Amsterdam and the links there will be important for the delivery of these therapies.

HOW DO YOU SEE THE FUTURE OF CELL THERAPY PROGRESSING?

First of all, let's think back to where we were two-and-a-half years ago. The consensus was that "although it looks promising, it remains to be seen whether anyone will be able to manufacture these products and successfully commercialize them." We've shown that it can be done and that bodes well for the future of our industry.

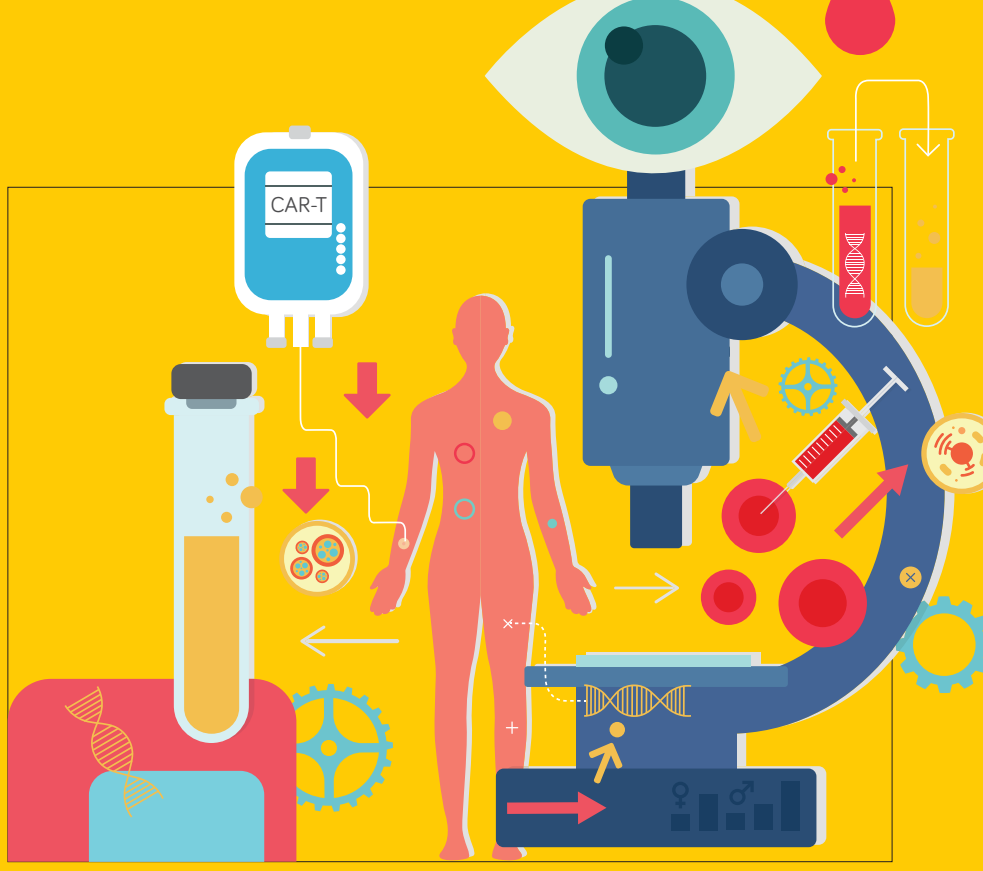
Looking ahead, we will find ways of automating autologous cell therapy manufacturing and improving the time it takes to qualify and deliver these therapies. But, ultimately, their potential is inherently limited by the need to transport, modify and deliver the therapy. I, therefore, believe that allogeneic therapy will have a huge role to play in the future and Kite has a number of initiatives in this area. On the development side, we're also going to see big advances in solid tumors. This won't be easy, but the potential is so vast that I believe we will find a way.

WHAT ABOUT KITE?

We want to get our products into more countries over the next few years, especially some of the smaller ones. I also believe we will have approvals in one or two new indications and that our turnaround times will be shorter – potentially around half of the time we are able to deliver these therapies at the moment.

DO YOU EVER FEEL THE PRESSURE BEING INVOLVED IN THE REALIZATION OF SUCH POTENTIAL FOR PATIENTS?

Pressure? Not exactly; rather a deep responsibility. I've spoken to patients that have been treated with our products and it is deeply moving to hear how it gave them another chance for life. But you do feel responsible for doing what you can to ensure that as many patients as possible also get the same opportunity. This is why we got into the industry in the first place. Though it's common to find yourself working on a therapy that, while beneficial to patients, perhaps there's another five similar products on the market, which limits your impact in the grand scheme of things. With cell and gene therapies, not only is your product treating patients with few (if any) options, it's also remarkably effective – curative in many cases. You do feel responsible but also fulfilled. It's an enjoyable area to work in!



DID YOU CATCH OUR CGT SUPPLEMENT?

It was remarkable to see the number of active cell and gene therapy clinical trials reach quadruple figures in 2018 – double the number in 2015 (1). But it is becoming clear that to translate clinical promise into real patient benefit, the industry must address the "goldrush on talent."

The Medicine Maker's cell and gene therapy supplement, published in December 2019, explored the skills gap in detail. Experts from the International Society for Cell and Gene Therapy argued that the industry needs more experienced workers at various levels – from lab technicians and manufacturing operators through to investors and business leaders – to help the field flourish:

- Emily Hopewell, Director of Cell and Gene Therapy Manufacturing at Indiana University and ISCT Interim Global Treasurer, USA, argued that with many cell and gene therapies skipping phase III trials entirely, academics must get to grips with GMP early. While Patrick Rivers, Principal, Aquilo Capital, and Co-Chair, ISCT Business Models & Investment Subcommittee, USA, advised investors to consider manufacturing and process development as critical parts of a product's profile.
- The regulatory aspect is essential to the development of the cell and gene therapy industry, according to Karen Nichols, VP Regulatory and Quality at Magenta Therapeutics, and Chief Regulatory Officer at ISCT. Regulation provides the crucial guidance and the guardrails that allow the technologies to demonstrate their safety and efficacy for broader application into humans.
- Bruce Levine, President Elect of ISCT, explained how ISCT is helping to tackle the talent gap through mentoring programs, training courses and public education programs.

Also included in the supplement:

- Vered Caplan, Orgenesis CEO, asks whether the daunting costs of cell and gene therapies be reduced if research hospitals developed and processed therapies in house to treat their patients.
- Philip W. Wills, from Catalent Paragon Gene Therapy, walks through the possibilities to improve gene therapy manufacturing processes and bring down costs.
- "New technology is emerging to help the gene therapy field progress," says Gabriel Festoc, from Polyplus-transfection. He points to new transfection technologies aimed at improving product titers and driving down costs.
- Miguel Forte, Chief Commercialization Officer at ISCT, believes TCRs are the way to fine-tune the way we target solid tumors.
- Can we move beyond Cas9 to reduce unintended off-target effects of CRISPR technology? Garrett Rettig, Integrated DNA Technologies (IDT), thinks so.
- Keith Thompson explains how the UK's Cell and Gene Therapy Catapult has played a significant role in building the strong advanced therapy ecosystem in the UK – the largest outside the USA.
- Ravi Nalliah, Chief Executive Officer and Cofounder of TrakCel, UK, explains his journey from biochemistry and molecular biology student, to chartered accountant, to founder of a CDMO focussed on providing cloud-based software to support supply chain management for the biotech industry.

To download the full supplement PDF, go to: https://bit.ly/2SiBrRo

Business

Economic drivers
Emerging trends
Business strategies

Hands Off the Goods

Aseptic filling is the final manufacturing step but it shouldn't be an afterthought. It's time to adopt closed, automated processes for the drugs of today and tomorrow.

By Chris Procyshyn

Back in 2000, while I was working at QLT (which merged with Aegerion in 2016), a problem became evident: the lack of process equipment suited for the job at hand.

QLT was partnered with Novartis at the time. One of our biggest products was Visudyne (verteporfin), but we were also making a host of other clinical products – many of which were very targeted and involved small batch sizes (which has become a major trend today). The production equipment, however, was tailored for the blockbuster era and large-scale manufacturing; after all, most injectable drugs, at the time, were mass manufactured in quantities of tens of millions. To address the problem, QLT built a pilot manufacturing facility – and, even today, I think the facility would still be considered innovative in terms of its footprint and the technological approaches that were taken. For me, it really showcased how much room there was for innovation in terms of manufacturing optimization. In particular, I saw huge potential for improving aseptic filling, which was largely ignored as other changes to manufacturing were made.

Sterile filling is the last part of the manufacturing equation – and often it is an afterthought as all the challenges of producing a new molecule have taken all the time, risk and effort contingency that the company allotted. Even if companies invest in updating their manufacturing processes, they will often still use the same, antiquated manual methods for filling that they have been using for decades. When I started out in the pharma industry, filling was an open process conducted manually in open cleanrooms. I wish I could say this was not the case anymore, but there are still countless companies that perform filling in this way. Many of us have been in the situation where a product is delayed because we cannot figure out the source of contamination – and often it stems from something as simple as an operator scratching their head at the wrong time. Some people in industry will also tell you that reject rates may go up (or down) when certain people are on vacation...

Automated systems for filling operations do exist, but are often not suited for today's smaller batches and the need for flexibility, such as being able to fill different containers (vials, syringes or cartridges) on the same machine without lengthy downtime.

I talked about the issue a great deal with one of my co-workers at the time, Ross Gold. And in 2007, we left our jobs in biopharma with the aim of designing a new form of aseptic processing equipment. We wanted to make new, optimized and automated systems for this field that did away with manual filling, and that were designed to cope with smaller batch sizes and frequent changeovers. In other words, we wanted to design equipment that would be fit for the future.

The end result was the founding of our company, Vanrx. Today, I am the CEO and Ross is Vice President of Tech Services.

Learning to become machine makers

Ross and I had been involved in many projects involving the purchase and installation of new equipment. After all the frustration from that, we felt a sense of responsibility to find a way to get the industry to use technology to lower risk and deliver more. The first thing we realized was that pharma is not the only regulated industry delivery critical clean technologies to the world. Semiconductor wafer clean processes can run for 30 days or more in continuous production using work cells. The wafer is passed from machine to machine within something called a FOUP, a front opening unified pod, and the wafer never sees human intervention throughout its whole production process. In other words, it's a completely closed process. As a result, you have clean conditions, high productivity, and great quality. These work cells are standard machines – you do not scale up by making a faster machine; you scale out by adding more machines. A semiconductor facility is full of the same systems duplicated over and over in rows to increase production. If more production is required, the semiconductor company builds a new warehouse and adds more work cells.

"It can be difficult to propose new regulations to force a dramatic shift away from manual processes."

Could this be applied to pharma? Ross and I spent a while trying to figure this out and eventually centered on the development of robotic, gloveless isolator systems that could be used as aseptic filling work cells. Gloveless means there is no human interaction at all, but to do this we couldn't just take a normal isolator design and remove the glove – we had to completely redesign the filling process. And that's the crux of the issue when it comes to automation – you need to design


vanr

a system and process that is robust enough to not require human intervention.

It was also important for us to develop systems that were standardized, reproducible and predictable. In the highly-efficient aviation industry, everything is standardized, certified, and produced in mass to bring down costs and improve transferability. In pharma, every equipment project is akin to a NASA Apollo program. Most systems are custom one-offs and, therefore, very expensive. In addition, not all vendors really understand the customer's process requirements. An equipment vendor will ask, "What do you want us to build?" If you are an aseptic processing expert, your experience could lie in regulatory and quality, but you probably will not have designed machines before. Do you really know what you want or the questions you should be asking? And if you forget something it could mean big trouble for your budget. It's like building a house. You may know what house you want, but you are unlikely to know how a house is built and may end up forgetting something obvious. Is this your fault? Or the fault of the builder who didn't understand your needs? Either way, the end result is an unsatisfactory experience and an unoptimized (and expensive) system.

Earlier, I described the problem of manual process and operator variability. At a conference, I remember hearing many companies complaining about inadequate operators. I pointed out that there are also a lot of smart operators out there making up for badly engineered processes…

Buying a car, on the other hand, tends to

be an easy process. You sit in the car; you try the car and you look at the price. If that's all good, you buy the car. And what you receive will be identical to the car you viewed. Would it not be great if buying pharma processing equipment was the same? Imagine a standard filling system flexible enough to suit a variety of requirements, and that can be built, installed and validated in less than a year. Equipment like that is where the future of the industry lies.

The pharma industry's appetite for risk – and innovation – is low. Standardization actually helps with this as you can see the performance before you buy, and know that the machine you purchase will be the same (just like that car). And that helped us to get Vanrx off the ground – we were not the only folks who had realized that something had to change in the industry and many companies told us they were desperate for new aseptic processing technology. However, pharma is still reluctant to change – particularly when it comes to aseptic filling. Many companies also told us that, as regulators didn't have an issue with their current processes, they were not going to change them. But then came shutdown after shutdown by FDA because of problems at aseptic filling facilities. It turned out regulators did have an issue, but the scale of the problem threatened to seriously impact the health system with the full extent of enforcement; agencies were concerned that without viable alternatives, they could not leave patients without the drugs they needed. Even today, however, the effects of some drug shortages attributed to this is being felt.

It was frustrating because change is not out of character for pharma. On the research side, if you have a new molecule – a molecule like no other molecule – the seas will part and an enormous amount of effort will go into designing the right processes for that molecule.

It can be difficult to propose new regulations to force a dramatic shift away from manual processes, when so many companies perform aseptic filling in the same manual way – and it could lead to temporary production delays or shortages. But regulators will tell you that it is heartbreaking to see a revolutionary new medicine made with cutting-edge technology being filled by someone with gloves. Not only are a lot of biopharmaceuticals filled this way, but so are cell and gene therapies – the most groundbreaking therapies of our day. More and more cell and gene therapies are entering clinical development – and, one day, processing these therapies will become the norm. But we must do better than filling them with gloves.

Facing the future

Despite the challenges over the years, I'm proud to say that Vanrx is gaining momentum. Today, we have a number of installations in major markets all over the world. In all the media fills that have been performed on our machines, there has never been a case of contamination. Many companies we have been working with went from installation to their first GMP batch ahead of schedule – an uncommon event when it comes to installing new processes or equipment in pharma. I think this example highlights why innovation in equipment is so important – it can make a real difference on the efficiency and cost of drug manufacturing.

There are times when I miss the drug development aspect of the industry, particularly the challenges and complexities involved. But I also feel that I need to do my part to fix some of the issues. And aseptic processing is long overdue for innovation. Drug shortages are a huge problem – and many of these issues come from aseptic processes (particularly processes performed manually). I've spoken to clinicians, who tell me how difficult it is for them to tell patients that they won't get access to a much-needed drug. A medical oncologist at a university told me that her students see drug shortages as "normal." It makes her so angry; she wishes she could take manufacturing people and force them to confront the patients who are affected.

Deep down, we all know what needs to change. We should not just sit back and wait for someone else to enact or enforce change. We should all consider how we can help improve our industry.

Chris Procyshyn is CEO and Co-Founder at Vanrx, Canada

What the Brexit Transition Period Means for Pharma

The "standstill" transition period begins as the Withdrawal Agreement clears the final hurdle

By James Strachan

Three-and-a-half years since the Brexit vote, the UK has left the EU – with a deal. There was no late drama as the European Parliament approved the Withdrawal Agreement by 621 votes to 49.

The UK now enters a "transition period." Although the UK will have no MEPs, no Commissioner, and no seat at the EU Council; EU law will continue to apply in the UK. And that means companies can continue UK batch release testing and qualified person (QP) certification; marketing authorization (MA) holders and QPs, and QPPVs can continue to be based in the UK and access EU markets; manufacturing and distribution licences will continue to be recognized by the EU and vice versa, as will inspections; and UK-based firms can continue to apply for MAs via either the centralized or decentralized procedure (1).

The MHRA will not be able to participate as a "lead Member State" or vote on new MA applications within the EMA, but it "may attend EMA and EU committees and any groups where there is a UK interest, or where relevant to the EU," according to the UK government's advice (1). As of July 2019, the exact nature of this participation was still up for discussion (2).

The transition period will last until December 31, 2020, unless the UK-EU Joint Committee decides to extend the transition period by up to two years; however, the length of any extension must be signed off before July 1, 2020. Notably, the UK government has made a legislative commitment not to agree to any extension, which could only be reversed through new legislation (3).

Trade negotiations will soon begin, but with just 11 months until the end of the transition period, there is a risk of failure, whereby the UK and EU would effectively trade under WTO rules. The exception is Northern Ireland, which will be obliged to align with specific EU rules, such as technical regulation of goods, and the EU's Union Customs Code – eliminating regulatory or customs checks between Northern Ireland and the Republic of Ireland. But this also

"As Michelle Barnier, the EU's chief negotiator, said in a recent speech, '[The UK] has chosen to create two regulatory spaces. This makes frictionless trade impossible. It makes checks indispensable.'"

means that although Northern Ireland will remain part of the UK's customs territory, customs checks and controls will apply for goods moving from Great Britain to Northern Ireland (4).

"Northern Ireland could become a gateway to the EU single market, for example, by continuing batch release testing and QP certification," says Wolfgang Schmitt, Administration Manager for the European QP Association (EQPA). "But there may be border checks on medicines moving from Great Britain to Northern Ireland. Plus, the UK will enforce EU rules in Northern Ireland, with EU officials observing and providing input."

"Hopefully, there will be a Mutual Recognition Agreement for the QP release by the end of the transition period," says Sascha Sonnenberg, Global Head Business Development at Sharp, a contract clinical, manufacturing, packaging and technology service provider.

"To avoid any issues, most companies operating in this area have already qualified or set up their own EU-based depots and established QP-to-QP agreements/declarations between a UK and EU based QP," he says. "But some have decided to leave their material in the UK and only transfer to the EU depending on the agreement both parties put in place."

Regardless of whether a deal is agreed by December 2020, it seems almost certain that the pharma industry will face a new trading environment. As Michelle Barnier, the EU's chief negotiator, said in a recent speech, "[The UK] has chosen to create two regulatory spaces. This makes frictionless trade impossible. It makes checks indispensable (5)."

Batch Release in Transition

During the lead-up to Brexit – with a no-deal outcome on the cards – companies were advised to transfer their batch release sites listed in their MAs to the EU. In a recent statement, the European QP Association (EQPA) claimed that for such products, the role of the UK QP would be limited to "confirmation" – a signed statement by a QP that a process or test has been conducted in accordance with GMP (7) – during the transition period (8).

"If the MA was changed (via "variation") to a new site in the EU, the UK QP will initially certify the products, but the final certification will be done by an EU-based QP," says Schmitt. "Of course, if the MA lists a site in the UK for final batch certification, the certification by the UK QP would still be acceptable during the transition phase."

This means, according to Elisabeth Lackner, an EU-based QP, CEO of ABF, and Global Head EVP of GBA Group Pharma; "a UK QP will be limited to 'confirming' batch release certification and not authorized to make the release decision alone. The UK QP release will not be equivalent to a QP release in the EU 27."

"This is perfectly correct – it centers around the marketing authorization," says Steve Girdlestone, UK-based QP and Head of Quality at Sharp Clinical Services. "The guidance based on a potential no-deal Brexit was that companies with a licenced product outside of the EU (i.e. the UK) needed to change and register that product so that it became a licensed product within the EU. This requires a formal release by a QP resident in Europe."

Girdlestone points out that many pharmaceutical companies, particularly the large ones, started that process and are now in a situation where their drugs are released by QPs resident in the EU. "Most have either opened offices or purchased facilities so that they can conduct their business from those sites," he says. "For example, there's a company in Ireland that has a registered office there and they will take the certification of the UK QP and translate that into a batch release originating from Europe. Often, this will be a "re-certification" of the work already undertaken by the UK QP." Girdlestone says that this is being challenged in certain quarters of the industry, however. "Some are saying this shouldn't be acceptable, even though it's supported by QP-to-QP agreements between sites."

"But as far as the transition goes, we operate as if we were still part of the European Union," says Girdlestone. "In fact, prior to the transition period coming into effect (while were still part of the EU) we were having issues with third party declarations issued by European QPs, with push-back from some regulatory bodies," says Girdlestone. "But since the UK entered into the transition period, one of the countries has changed their stance and we're no longer having issues with them."

Girdlestone points out that if the UK leaves the transition period without a deal, companies that have not yet transferred their MA and batch release site to the EU will need to do so. "But the reverse is also true," he says. "If European-based companies want to market their products in the UK, they will need marketing authorization in the UK."

But Michael Warren from the BIA is hoping for close regulatory alignment with the EU. "The briefings we've had from government ministers over the past few weeks makes it clear that the government is still keen to hold to the position set out in the political declaration, which means exploring cooperation with the EMA," he said (6). "I think the key point here is that, as the Chancellor said […] where it's in the UK's interest to align, the UK will align and we're very clear that it is very much in the UK's interest to align – both for the safety of patients and in the interests of our world leading life science industry. So I think that does leave the door open for a side deal on prioritizing life sciences as a protocol to a broader FTA."

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Catching Up with Innovation

What's the latest from the winner of The Medicine Maker 2018 Innovation Awards?

We recently published The Medicine Maker 2019 Innovation Awards – and we are currently asking you to vote for your favorite technology of 2019 online: http://tmm.txp.to/vote-innovation19.

While the votes are flooding in, we caught up with our winner from 2018 – Catalent. The company's Zydis Ultra taste masking technology won last year's public vote. Zydis Ultra allows for increased drug loading and greater taste masking capabilities compared with the company's traditional Zydis orally dissolving tablet. The API is coated using acoustic mixing, which bombards API particles with a micronized polymer to form a very thin (tens of microns) coating. The result? Taste masking without any impact on oral disintegration time or gastrointestinal dissolution performance.

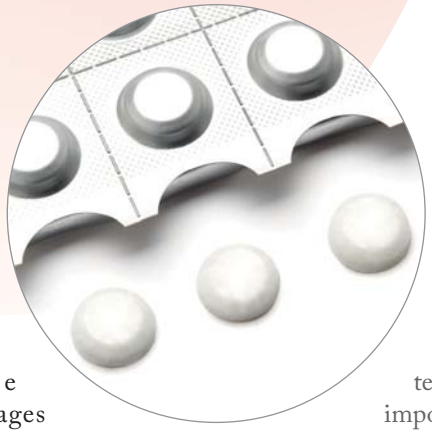
We asked Catalent to give us an update on the technology – and its plans for the future.

What has the past year been like for Zydis Ultra?

Excitement around the new technology continued throughout the past year. As we gained more interest from customers, we announced that we were to invest $27 million to expand the API coating facility for Zydis Ultra. The expansion is expected to grow the business from producing one billion orally disintegrating tablets annually to two billion. We also plan to add 100 more employees at the Swindon, UK, site in the next two years.

What do customers like about the technology?

The development of Zydis Ultra builds on the existing advantages of Zydis, such as its convenience and patient compliance, and allows the formulation of dosages with up to four times the drug loading. The taste-masking capabilities of the technology means that drugs that exhibit unpleasant properties, such as bitterness, can be overcome. It also broadens the range of drug molecules that can be used with our Zydis technology.



What recent projects or deals can you tell us about?

In the last few months, we have announced two new partnerships with drug developers. The first, Cycle Pharmaceuticals, includes three Zydis Ultra projects and one conventional Zydis project in rare metabolic and neurological disorders. The company identified Zydis as a method of improving the experience of patients, who often suffer from serious medical conditions, and reducing the pill burden.

The second agreement, with Ethicann Pharmaceuticals, aims to develop a new combination pharmaceutical-grade cannabidiol and tetrahydrocannabinol product that, if approved, would treat patients suffering from multiple sclerosis spasticity, and allow patients to self-dose – a significant advantage over other drug products.

What are your hopes for the future of the technology?

Our hope is to continue to increase the number of projects with partners, and to expand the range of drugs that are commercialized using the technology. We are also continuing to work on fast dissolve formulations of large molecule allergens, viral vaccines, and peptides through the Zydis Bio work, which has been ongoing for several years.

Why is innovation in smart and patient-friendly formulation technologies so important?

One of the foundations of our business is the "patient first" philosophy. We believe that developments in dose form design and drug delivery technologies should be focused on improving patients' outcomes and experiences. Patient-centric dose form design is especially important when it comes to specific patient populations with unique needs, such as pediatrics and geriatrics. In these instances, Zydis technology offers advantages as the tablet disperses almost instantly in the mouth without water, overcoming issues with swallowing.

Additionally, there are a number of other technologies that can be used to improve oral dose forms and address patient and molecule needs, including controlled release tablets that can alter the duration of action of a dose; smaller tablets to improve swallowability, and numerous bioavailability enhancement formulations to potentially reduce the number of tablets taken by patients each day.

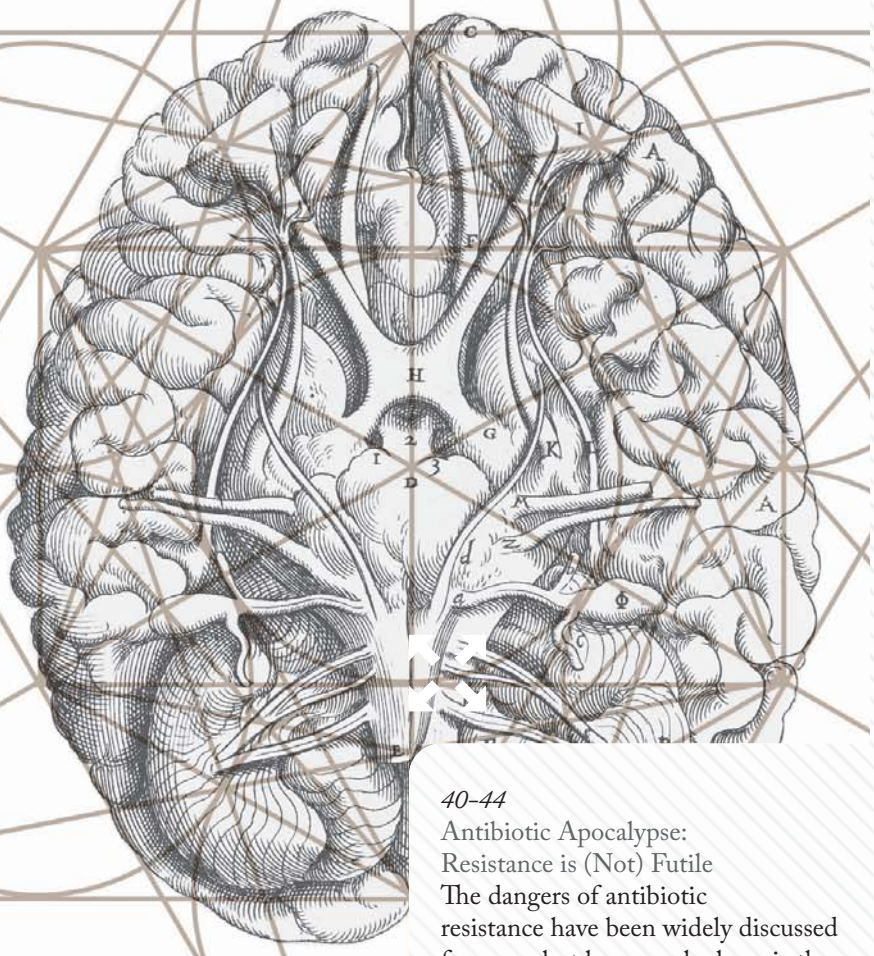
What else did the company achieve in 2019?

In 2019, the company expanded its technology offerings into gene therapy through the $1.2 billion acquisition of Paragon Bioservices – a leading viral vector development and manufacturing partner for gene therapies. Gene therapy is now one of the fastest-growing areas in healthcare.

In addition, we made a number of investments in our global network of facilities in 2019 that will come on line in 2020 and beyond, including the Swindon site and the acquisition of a site in Anagni, Italy. The Anagni site will act as a European hub for the company's biologics business and also offer oral solid dose development and manufacturing capabilities.

NextGen

R&D pipeline
New technology
Future trends



Antibiotic Apocalypse: Resistance Is (Not) Futile

Threatening global economies, healthcare systems and human lives, the issue of antibiotic resistance is ever-present. But how much closer are we to resolving the problem?

By Maryam Mahdi

Antimicrobial resistance (AMR) affects societies across the world. Each year, an estimated 700,000 people die worldwide as a result of drug resistant bacterial infections (1). The repercussions for public health are clear – but there are also economic implications; estimates suggest that 3.8 percent of the world's annual GDP could be lost by 2050 in a high-AMR scenario (where a significant number of antibiotics fail to treat bacterial infections) with an annual loss of $3.4 trillion by 2030 (2).

The solution to this far-reaching issue? Well, it is far from straightforward. There may well be a pressing need to regenerate a sustainable pipeline of new drugs to combat AMR, but Andrew Edwards, a senior lecturer at Imperial College London, argues that current market conditions aren't suited to the development of antibiotics.

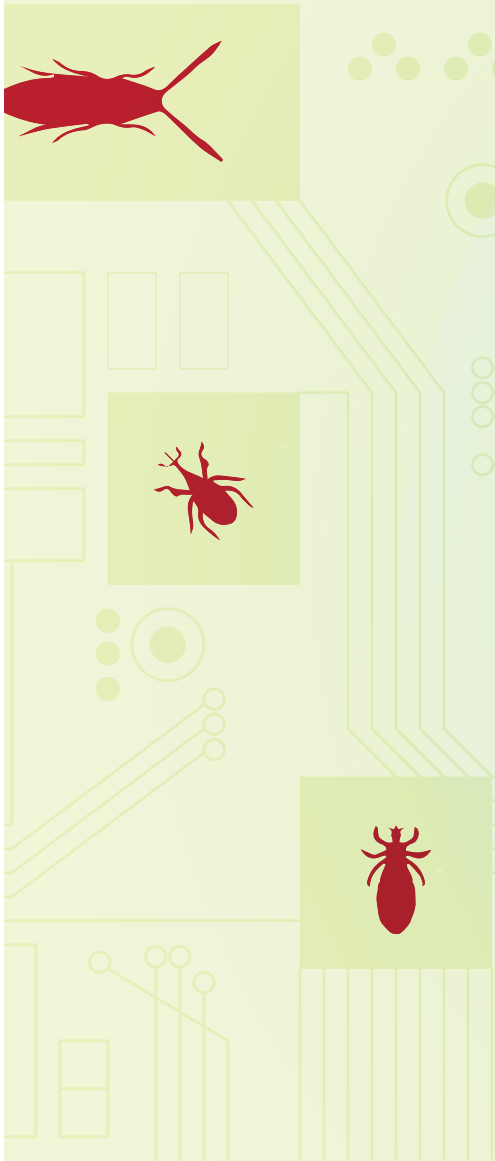
Make antibiotics great again

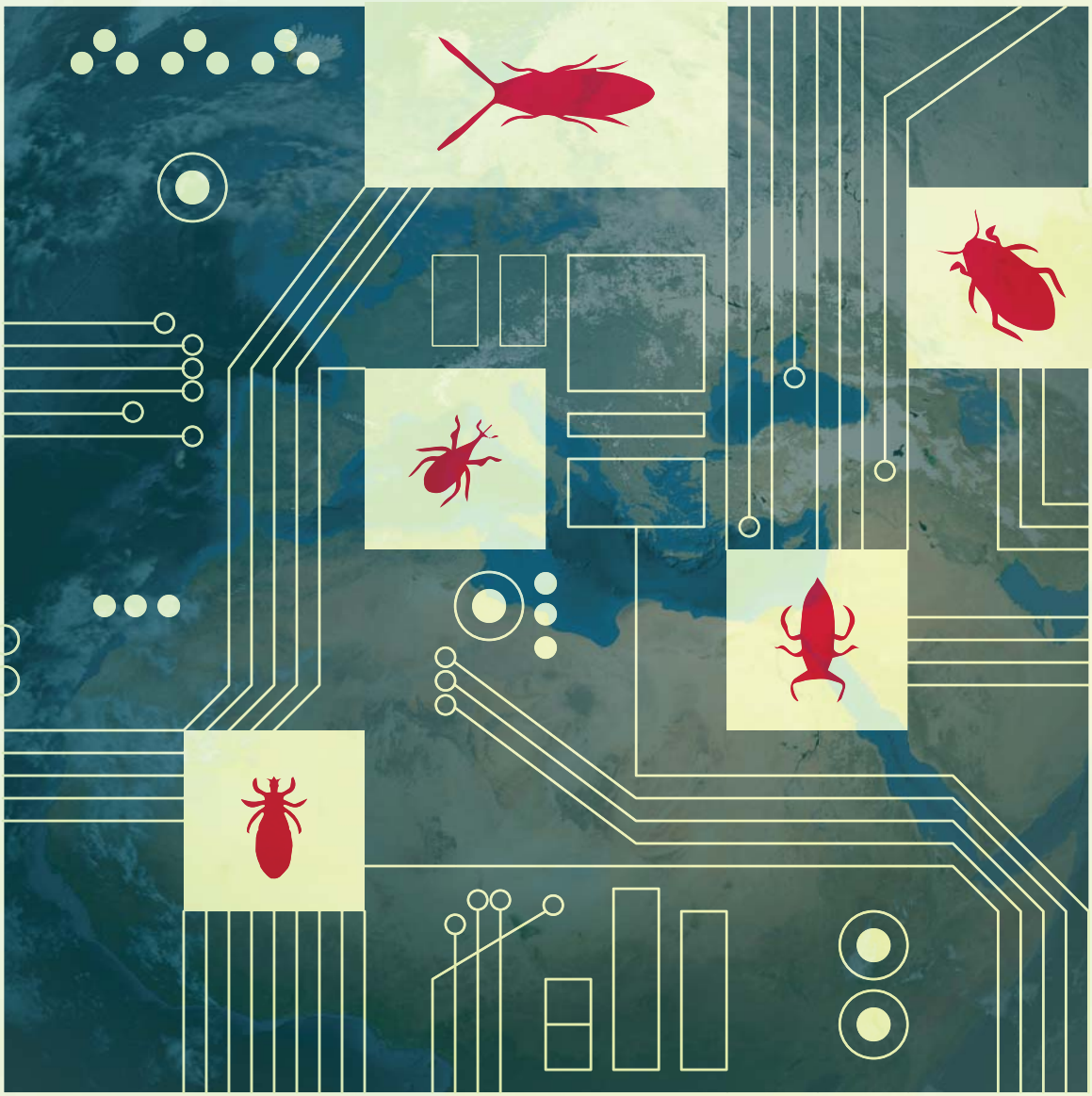
Roughly half of all antibiotics used today were discovered between the 1950s and 1970s (3). Today, developing new drugs has become more complex, time consuming, and expensive. Antibiotics typically have short treatment durations and the use of a new antibiotic would ideally only be used for patients who really need it, to help limit development of resistance. As Edwards explains, "The existing market is geared toward making medicines that can be used by as many patients as possible. By contrast, new antibiotics may be locked away and held in reserve only for infections caused by the most antibiotic resistant bacteria. Therefore, there are poor financial returns for companies considering pursuing them."

Another significant challenge is that many of the drugs entering the market are variations of existing products. Though they are relatively easy to produce, they are often susceptible to the same resistance mechanisms that were neutralized in previous iterations of these drugs. One essential component of the solution to the ongoing crisis, according to Edwards: "Investment in entirely different classes of antibiotics as well as more rapid diagnostics and vaccines."

Edwards also highlights a less obvious problem that prevents headway being made in the field: "Whilst high prices and host toxicity are seen as acceptable for cancer treatments, antibiotics are expected to be cheap and non-toxic.

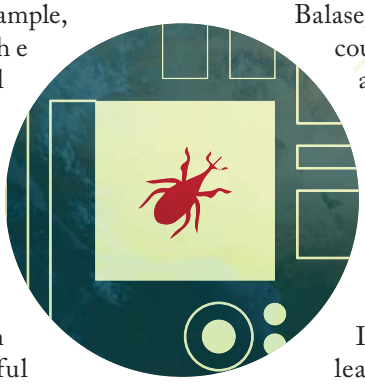
"Another significant challenge is that many of the drugs entering the market are variations of existing products."





And that means the development of antibiotics is expensive, risky, and poorly rewarded."

The current climate drives the need for alternatives to traditional business models; for example, incentivizing the development of novel products through approaches such as upfront funding, market entry rewards and transferrable exclusivity vouchers. With the latter example, an extension is granted to successful innovators of a new antibiotic that could be applied to an existing drug on a one-time basis. The extension would be tradeable, so an innovator could sell it to a company with a patent close to expiry.



Manica Balasegaram, Executive Director at The Global Antibiotic Research and Development Partnership (GARDP), a not-for-profit organization set up by the WHO and Drugs for Neglected Diseases initiative (DNDi), explains that finding the right balance of these incentives is key to addressing the issue. However, he also adds that transferable exclusivity vouchers are perceived as "too costly or politically non-viable for governments." He believes that the public sector would need to play a role in making such initiatives successful.

In an attempt to determine if one of these alternative solutions had real potential, the UK became the first country in the world to start a trial of a new way of paying for antibiotics as part of its National Action Plan. The trial aims to test a reimbursement approach that offers a defined revenue stream and secure access for existing and new antibiotics through the country's National Health Service. "The pilot project is definitely promising. But critical questions remain, including appropriate subscription rates, sustainable financing, qualifying criteria, and scalability," says Balasegaram. "Such incentives could be an economically and politically feasible way to help maintain an R&D ecosystem, particularly for SMEs and manufacturers."

According to the Association of the British Pharmaceutical Industry (ABPI), a leader in delivering the UK's action plan, the practical details of the model (including ensuring appropriate use) will be ironed out as the project progresses.

Though efforts are being made to transform the public sector's approach to antibiotic R&D, the private sector also needs to be rallied. And so, the AMR Review, chaired by Lord Jim O'Neill, stated that incentive models must be sufficient to sustain R&D across the full lifecycle of products to see long-term change to the pipeline of products available (4). However, a recent review of the progress made since the recommendation was implemented highlighted that there had been little movement by governments or the pharmaceutical industry (4). Lord O'Neill noted in an AMR Review report that both parties are seemingly waiting for the crisis to escalate before doing more. The lack of action not only affects the readiness of tools required to address rising resistance, but also has implications on the profitability of industry, given that drug resistance threatens the viability of current product markets. The review called for greater efforts on all sides: "Unless key players are prepared to behave differently and make bolder decisions, the challenge is never going to be solved, whether that be policymakers, drug companies, doctors, farmers and, ultimately, all eight billion of us (4)."

"Though efforts are being made to transform the public sector's approach to antibiotic R&D, the private sector also needs to be rallied."

Bryan Deane, New Medicines and Data Policy Director at the ABPI, notes that despite the withdrawal of more large companies and two biotech bankruptcies, the pharma industry has managed to sustain the involvement of over 50 companies (5) since the formation of the AMR Industry Alliance (a private sector coalition set up to provide sustainable solutions to the AMR crisis) in 2016. However, he agrees that more investment and better incentivization is needed. "Although the UK is very good at infection prevention and control, it can take over ten years to develop a new medicine - the whole point of getting things right now, in terms of finding new antibiotics, is to be ready to prevent the disaster scenario from occurring."

Deane and Balasegaram agree that, if mechanisms are developed to shift accountability to governments working

directly with industry, the chance of implementation and desperately needed investment will increase. The Global Antibiotic Research & Development Partnership (GARDP), whose aim is to deliver five new treatments by 2025, was set up to help foster partnerships between the public and private sectors and is one of many organizations working to tackle AMR on an international scale. Other initiatives include the Davos Declaration; signed by over 100 companies and associations, the declaration represents an industry-wide commitment to deliver sustainable solutions to AMR on an international scale (6). But, despite marking a significant turning point in the industry's battle against AMR, the market for antibiotics has continued to deteriorate.

Beyond borders

In low- and middle-income countries (LMICs) the consequences of AMR are more severe but less well understood, because data on drug resistance is lacking. "Proxy indicators point to a more dire situation than that faced in Europe and North America. It is in these LMICs where several issues – the lack of access to both new and old antibiotics, regulatory challenges, as well as lack of infection prevention and control – will hit hardest and show the first and most devastating impact of drug resistance," explains Balasegaram.

For LMICs, other major challenges to handling the crisis are cost and education. Second- and third- line antibiotics are simply too expensive for developing countries to justify – a problem that is exacerbated by the overzealous sale and use of over-the-counter antimicrobials. Though awareness is increasing, thanks to initiatives like World Antibiotic Awareness Week (which was first launched in 2015), more needs to be done to improve the public's understanding of AMR (7).

While the AMR Alliance report (5) documents further progress on access, this must go hand-in-hand with education to ensure appropriate use.

"No single country or organization is going to solve this problem on its own. We all have to recognize that, by working together, we are more than a sum of our parts," says Deane. "Ensuring the appropriate use of antibiotics and implementation of

"Though there are still hurdles to overcome in the fight against AMR, many experts remain optimistic about the future."

action plans is essential to preventing the situation from worsening while we investigate new antibiotics and even new approaches."

For Edwards, an important aspect to tackling AMR is collaboration between industry and academia. Bridging the gap between these two circles has conventionally been challenging, but UK Research and Innovation (UKRI), a non-governmental organization that directs research and innovation funding, is facilitating closer cooperation and collaboration via dedicated funding streams.

"Academia is investigating a huge number of novel therapeutic and diagnostic approaches that could prove to be key in battling antibiotic resistance. However, it's very hard for academics and universities to efficiently translate this research into medicines and diagnostic tools." explains Edwards. "This is largely because translational work requires expensive and technically demanding PK/PD and toxicology work, which is hard to find funding for. But industry excels in these areas; this makes it essential that academics and industry work together to identify and develop the solutions needed to tackle antibiotic resistance."

The (not so) bleak future

Though there are still hurdles to overcome in the fight against AMR, many experts remain optimistic about the future. Deane comments that, though the UK has robust initiatives in place to help address AMR, scientists from around the globe will be the ones to solve the problem.

Balasegaram shares the same opinion: "I believe that collectively we can deliver new and improved treatments that will save lives. The know-how and resources exist. What is needed is the political will and urgency, at national and international levels, to bring these two elements together to deliver results."

How long before we see those results? Well, that's a question few would attempt to answer. What we do know is that bacteria are constantly evolving – and they don't stop at borders. But as the number of projects in the pipeline continues to grow, so too do our chances of facing off the crisis.

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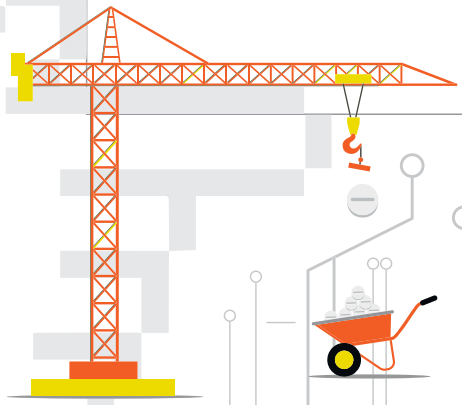

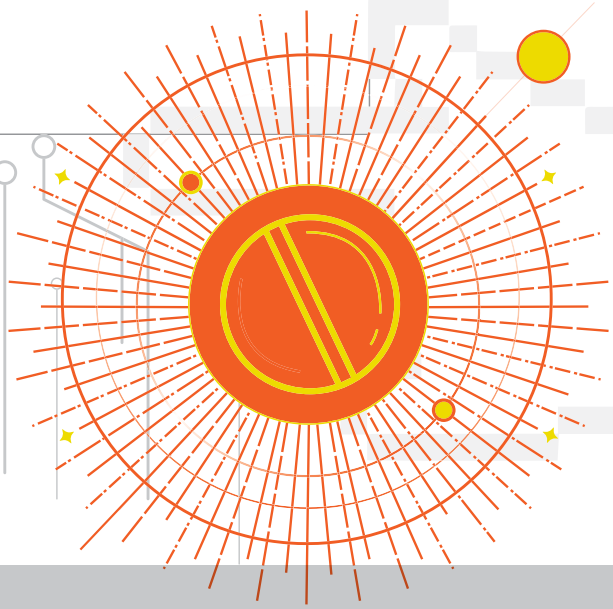

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A Matter of Cellular Integrity

A cell-free biologic could act as a platform therapeutic for a variety of serious diseases

By Maryam Mahdi

The process of normal wound healing is complex, relying on an exquisitely choreographed interaction between a variety of bioactive proteins and other factors. When wound healing goes awry, conventional "one-drug, one-target" approaches have struggled to restore the intricate balance.

But back in the 1970s, scarless fetal wound healing was first observed following in utero surgeries as a treatment for spina bifida. The phenomenon has been attributed to the numerous growth factors and cytokines secreted by the amnion epithelial cell layer of the placenta; notably, fetal skin contains a higher ratio of collagen type III to collagen type I compared with adult skin. The findings pointed to powerful wound healing capabilities, and scientists soon began to investigate numerous components of the fetal environment.

Not surprisingly, there has been significant interest in fully harnessing these healing properties for therapeutic uses. For example, Noveome Biotherapeutics is developing a novel platform biologic, ST266, as a therapeutic for diverse disease indications. ST266 is a cell-free biologic secreted by a novel population of select amnion-derived epithelial cells, which have been collected from full-term placentas that are normally discarded after birth. These cells are cultured using a proprietary method and produce many of the biological factors found in amniotic fluid that may be responsible for the remarkable healing capabilities and lack of scarring observed following in utero fetal surgery.

Here, we speak to Noveome's Larry Brown, Executive of Research & Development/Chief Scientific Officer and Randall Rupp, Executive Vice President of Manufacturing and Development, to find out more about the clinical-stage company and its objectives.

What does Noveome hope to achieve?

Larry Brown: In short, we're focusing on biotherapeutics for the promotion and restoration of cellular integrity of inflamed or damaged tissues. Our lead candidate is ST266, which contains hundreds of biologically active molecules, including proteins and other biomolecules. ST266 has potential in a number of therapeutic areas including neuro-protection, ophthalmology, brain injury and dermatology. Many of these conditions currently have no or limited therapeutic options, in part because they are often too complex to be treated with traditional one-drug, one-target therapies. Our results thus far are exciting and may lead to promising treatments for currently underserved patients.

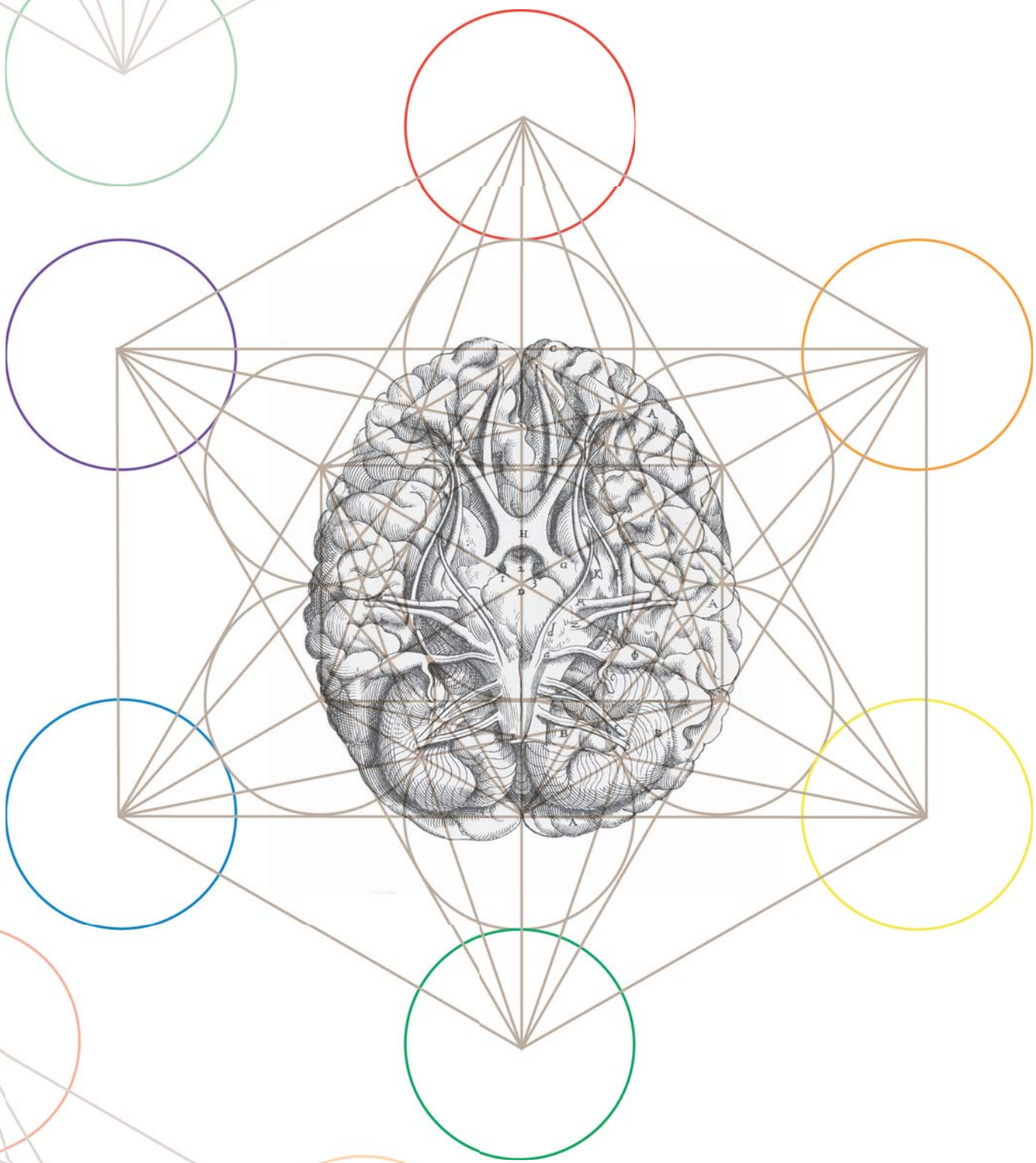
What are the key events in the evolution of Noveome?

Randall Rupp: In the company's early days, we sent the cells from which ST266 would ultimately be derived to different labs to see what effect they would have in their model systems. The Walter Reed Army Institute of Research was among one of the first institutions that we partnered with, testing our product in traumatic brain injury models in rats. In their experiments, they inserted and inflated balloon catheters into the brains of these animals so that they lost their ability to walk. When our cells were introduced, they regained their motor ability and the rats' brain tissue underwent healing. Interestingly, they found that if the cells were introduced on the opposite side of the brain from the wound, the wound was still repaired, indicating that it was the secreted product of the cells rather than the cells themselves that had the wound healing properties. In other words, the result suggested that the cells were only facilitating the delivery of the secretome to the damaged tissue rather than affecting the wound healing process themselves. And it led us to test the effects of the cell-secreted products alone and encouraged us to continue developing ST266.

What main disease areas are you looking into – and what are the challenges?

Brown: Neuro-ophthalmology, brain injury and neurodegenerative diseases are important areas we are focusing on. Injuries and diseases to the brain and related sensory organ structures such as the optic nerve can't be treated using conventional oral or injectable drug delivery systems. This is because the drugs are either too large or are not capable of circumventing the blood-brain barrier. When we conducted traumatic brain injury studies at Walter Reed

"In short, we're focusing on biotherapeutics for the promotion and restoration of cellular integrity of inflamed or damaged tissues."



Army Institute of Research, ST266 was directly administered into the brain. Yes, we observed positive functional neuroprotective and anti-inflammatory effects; however, direct injection into the brain is extremely invasive and an impractical delivery route. Therefore, we proposed using a targeted intranasal delivery that would be able to bypass the blood-brain barrier.

We found that when ST266 was administered to the nasal passages in rats, it was absorbed by the olfactory nerves in the very back of the nose. The olfactory nerves penetrate the cribriform plate allowing the ST266 to bypass the blood-brain barrier and be delivered to the optic nerve and brain. However, depositing ST266 to the back of the nose in humans requires a specialized intranasal delivery device. Noveome demonstrated that it could deliver radioactively labeled ST266 to the brain of non-human primates (monkeys) using an intranasal delivery device developed by SipNose LLC, an Israeli medical device company. We observed that the highest ST266 concentration was in the optic nerve.

The optic nerve deposition led us to explore neuro-ophthalmic conditions. We worked with Kenneth Shindler, Associate Professor of Ophthalmology at the University of Pennsylvania Medical School. Optic neuritis is inflammation of the optic nerve accompanied by vision loss and is often the presenting symptom of multiple sclerosis. Shindler's research group demonstrated that intranasal ST266 reversed retinal ganglion cell loss, preserved visual acuity and significantly reduced demyelination of optic nerves in an animal model of optic neuritis. As a result, we have begun human trials of targeted intranasal ST266 using the SipNose device.

In addition to leveraging this targeted intranasal approach to address "back of the eye" conditions, we have also administered ST266 topically to the eye, skin, and oral mucosa to treat a diverse range of other disease indications. For example, ST266 was shown to help prevent UV light burn damage and reduce the DNA cross-linking associated with UV damage to the skin.

"In our view, it's important that we keep the focus on disease indications where there is a lack of effective treatment."

Rupp: It's also important to consider that there are many ophthalmic disorders whose needs are currently poorly or unmet. For example, currently available products that deliver growth factors to the vitreous of the eye are expensive and require uncomfortable intravitreal injection. We're also working to address these issues with products in our pipeline.

What were the most exciting moments for the company in 2019?

Rupp: First, in June 2019, we began a phase two open-label trial for ST266 in patients with persistent corneal epithelial defects (PEDs). PEDs are the loss of the corneal epithelium through mechanical trauma, dryness, neurotropic disease or post-surgical change, especially in patients with medical impairments, such as diabetes. In these patient, promoting healing, reducing scarring, minimizing inflammation and retinopathy remains a clinical challenge. ST266 has been shown to promote corneal healing in rabbit studies. We hope that our ongoing phase II study will show efficacy and tolerability of ST266 in patients with PEDs and ultimately provide a therapeutic option they deserve. Second, in October 2019, we initiated a phase one open-label trial to establish the safety of ST266, when delivered intranasally in patients diagnosed with intraocular hypertension who have not yet developed optic nerve damage. We hope to expand this patient population to include all glaucoma suspects not just intraocular hypertension patients.

And what is Noveome looking forward to?

Brown: There is a lot of exciting research taking place in the biopharma industry as a whole, but in our view it's important that we keep our focus on disease indications where there is a lack of effective treatment. There are many patients that have spent years feeling neglected by the industry. We're excited that ST266 could be used for a variety of indications where patients have been underserved. As well as the areas mentioned above, a new focus for us is necrotizing enterocolitis (NEC). NEC is a devastating bacterial inflammatory disease that affects the intestine of premature infants and is the most common gastrointestinal emergency in neonatal intensive care units. The disease occurs in nearly 10 percent of premature infants and has a mortality rate of 32 percent – a rate that has not seen a decrease in the last three decades. We are currently conducting preclinical studies and are hopeful we can someday have an impact on this serious condition.

To date, 238 patients have been treated with ST266 in nine clinical trials in various indications. In all cases, ST266 demonstrated a strong safety profile with no reported drug-related serious adverse events. We are excited about both our current clinical trials and what the future holds.

Sharing Is Caring

Sitting Down With… Matthew Todd, Chair of Drug Discovery at University College London and founder of the Open Source Pharma movement.

What got you interested in science?

My interest was cultivated at home. Dad was an engineer who built bits of spaceships, and my mom taught physics – we would often talk about science at the dinner table. From a young age, I explored the idea of many careers in science, from dinosaur hunting to astronomy, but ended up focusing on organic chemistry. Throughout my academic career and numerous grant applications, however, the question underneath it all was always, "Are we working in the right way?"

Why did you feel there was a need for open source pharma?

The unfortunate public perception is that "big pharma" is just money-hungry. To some extent, this is true – big pharma are companies and they are obliged to make money, but this is just the way that business model works; to blame them for this is curious.

But it is also strange that, generally speaking, this system is the only one that generates the medicines we use. There are going to be times when big pharma does a really great job, and there will be other times when it struggles to deliver. Alternatives are never a bad thing. And that's why I like the idea of open source drug development – and why I founded Open Source Malaria, for example. We can't expect a big pharma company to operate in an open source way, but the industry is full of people who genuinely want to help patients, which means it is possible to open up a different kind of research process. With Open Source Malaria, the number and quality of contributions from people working in the pharma industry is unreal – Pfizer and GSK in particular have contributed significantly. Working for the Encyclopedia Britannica doesn't stop you from contributing to Wikipedia – and it doesn't mean you have to give up your job.

How has open source developed?

Our first project started in late 2004; we wanted to develop an optimized version of praziquantel with the WHO. We put some ideas online, hoping to replicate the "hive mind" that we were seeing throughout the Internet. But social media wasn't around at the time, so you couldn't spread ideas very easily. We didn't get much of a response. It's possible people thought we were crazy.

But we finally received a grant and got started in the lab. Still trying to tap into the hive mind, we deployed an online lab notebook in 2010 that anyone could contribute to. And it all kicked off… We received a lot of high-quality advice. For example, people in industry told us that our development plan would not work, so we changed our approach early to avoid wasting time and resources. Other contributors gave preliminary experimental results. Through contributions from strangers, we finished the project early and developed a very nice scientific solution.

For me, however, the project was an interesting demonstration of what happens when you open up research. With no protected intellectual property – and hence no possibility of a patent – people gave freely and quickly because the whole idea was uncomplicated. Since that first project, technology and social media have moved on enormously, so it's even easier to work with people today. Yet our open source projects are still unusual. There is no secrecy, and there are no patents – and there never will be.

What are you working on at the moment?

After the WHO project, Tim Wells, the Chief Scientific Officer of the Medicines for Malaria Venture (MMV), asked me what would happen if we were to use open source to develop new drugs, without patents? We talked about it a lot – and then decided to try it out, since doing can be faster than talking. We are now on our third and fourth open malaria series, having finished the first and abandoned the second. If we can get a molecule into Phase I trials, it will be the first time a molecule that has been "born open" has reached the clinical phase. It's a very challenging – and interesting – process. For some molecules, we have conflicting data but it's all in the open for everyone to see and to work through, meaning people can witness science as it really is, rather than after it's refined and packaged.

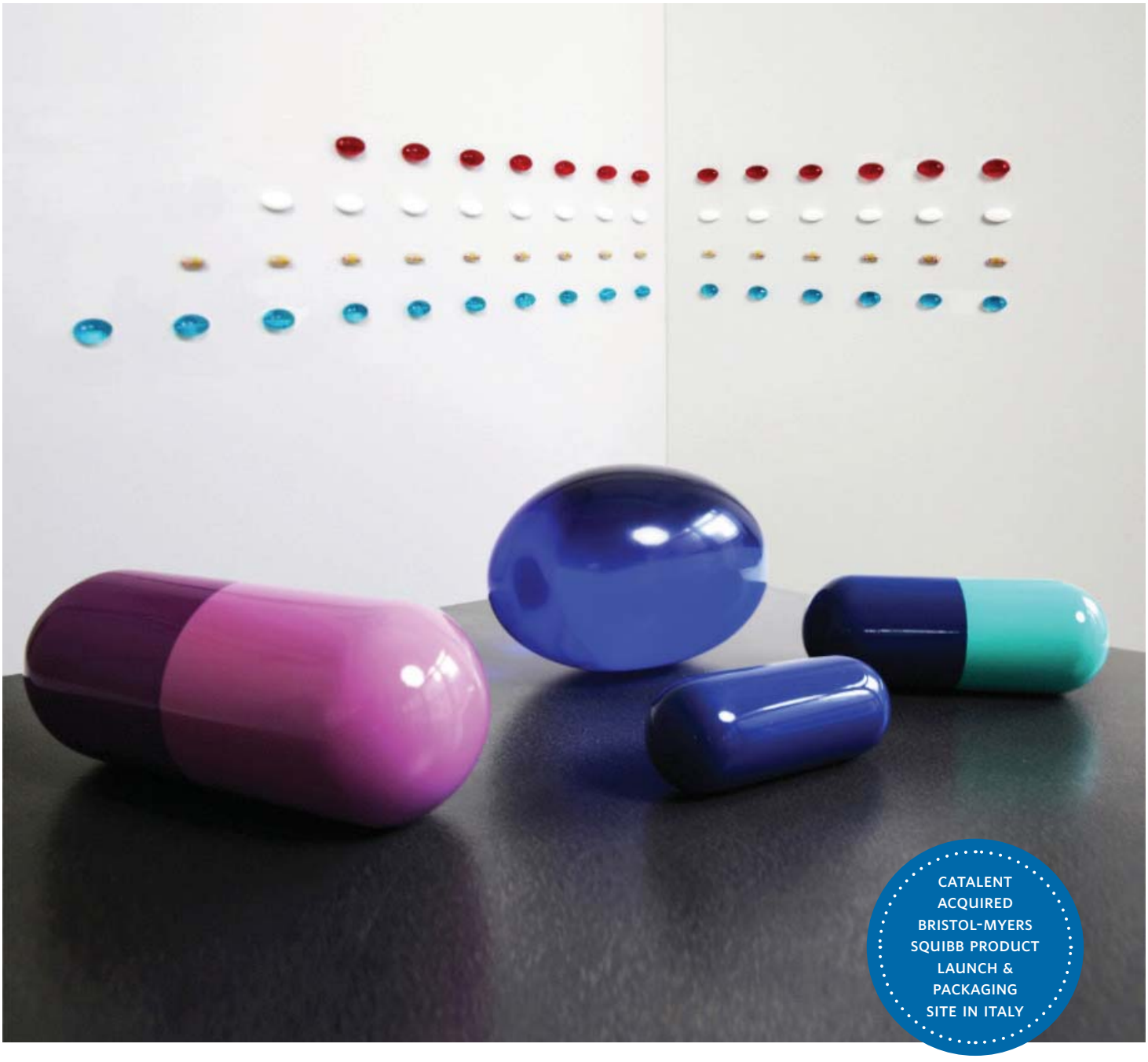
We've mirrored the Open Source Malaria project structure for mycetoma (a fungal infection) with the Drugs for Neglected Diseases Initiative (DNDi) in Geneva. It's not the big killer that malaria is, but it is genuinely neglected in that there are currently no good drugs to save people from treatment by amputation. There are also some open projects on the go with TB, which we started with GSK.

What's next for the open source movement?

I want to take open source pharma into new areas beyond neglected or tropical infections. I want to focus, for example, on rare diseases, where there's just no market; dementia, where there is a frightening lack of drugs; and on antibiotics, where big pharma is pulling out because of the tough economic model. Excitingly, the first open source antibiotics venture is underway – a fragment-based drug discovery project based on data that was acquired by teams at the Universities of Warwick and Oxford. If people are looking for a genuinely new way to deliver an antibiotic, this is it.

We also need to explore how open source drug discovery can be economically sustainable. Open Source Malaria is backed financially by people who don't require much return and because the medicine will be always be priced as low as possible, there is a weak economic incentive to compete with (or steal from) an open approach. But at the same time, you want to capture people's enthusiasm for their investment.

If we can establish the possible rules, platform, and financial model for open source drug development, then others can run their projects with such validated approaches. In the coming years, projects that have been paused, perhaps for financial reasons, can be put into the public domain as starting points. Imagine 50 different antibiotics projects where everyone, from senior pharma executives through to school children in science class, can make sure that the research is being done well. That's a future I'm excited about.



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