MAY 2020 # 65

the Medicine Maker™

Revving Up for the Revolution: Industry 4.0

Pharma is rapidly approaching a future of enhanced, data-driven manufacturing

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The Counterfeit COVID-19 Crisis

How fakers are taking advantage of the pandemic

COVID 19 has brought out the very best of the industry. Pharma companies seem to be moving faster – and collaborating more – than ever before. But every light creates a shadow. As pharma companies go to work, their arch-nemesis ups its game. Yes, counterfeiters are preying on a worried global population.

Counterfeit pharmaceuticals are a traditionally tricky problem to address. Manufacturers try to deter counterfeiters through clever formulation and packaging strategies, but the counterfeit pharmaceutical market is temptingly lucrative. For example, $1,000 invested in falsified drugs can result in profits of $500,000 – compared with profits of around $20,000 for heroin trafficking (1). The panic created by COVID-19 presents a huge opportunity for criminals as people flock online for medicines and personal protective equipment.

Interpol's annual Operation Pangea took place in March – and those involved noted a theme. Compared with 2018, there was an increase of around 18 percent in seizures of unauthorized antiviral medication, and an increase of more than 100 percent in seizures of unauthorized chloroquine (2). In addition, the operation discovered 2,000 online links advertising COVID-19 related items, and seized more than 34,000 counterfeit and substandard masks, as well as medicines advertised as "corona sprays, "coronavirus packages" and "coronavirus medicines."

High-profile individuals touting the benefits of certain medicines have compounded the issue; online demand for hydroxychloroquine surged 1000 percent after it was endorsed by Elon Musk and Donald Trump, as users explored websites such as Amazon, eBay and Walmart for the drug (3).

Panicked consumers are not the only party being exploited by criminal gangs – companies are also at risk. Interpol recently described, in detail, how one company became victim to an elaborate scam involving an order of masks (4). The moral of the story: we must all be super vigilant.

Just as pharma companies are stepping up to develop new COVID-19 treatments, we are also likely to see more partnerships aimed at stemming counterfeits. In the USA, changes are already afoot, with 3M, Amazon and Pfizer collaborating with US Immigration and Customs Enforcement to stem the flood of counterfeit COVID-19 products. Even during a pandemic, counterfeiters do not rest – and neither should efforts to fight them.

Stephanie Sutton
Editor

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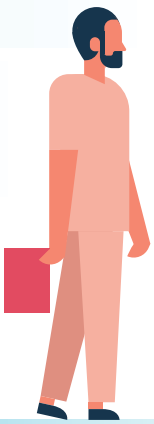
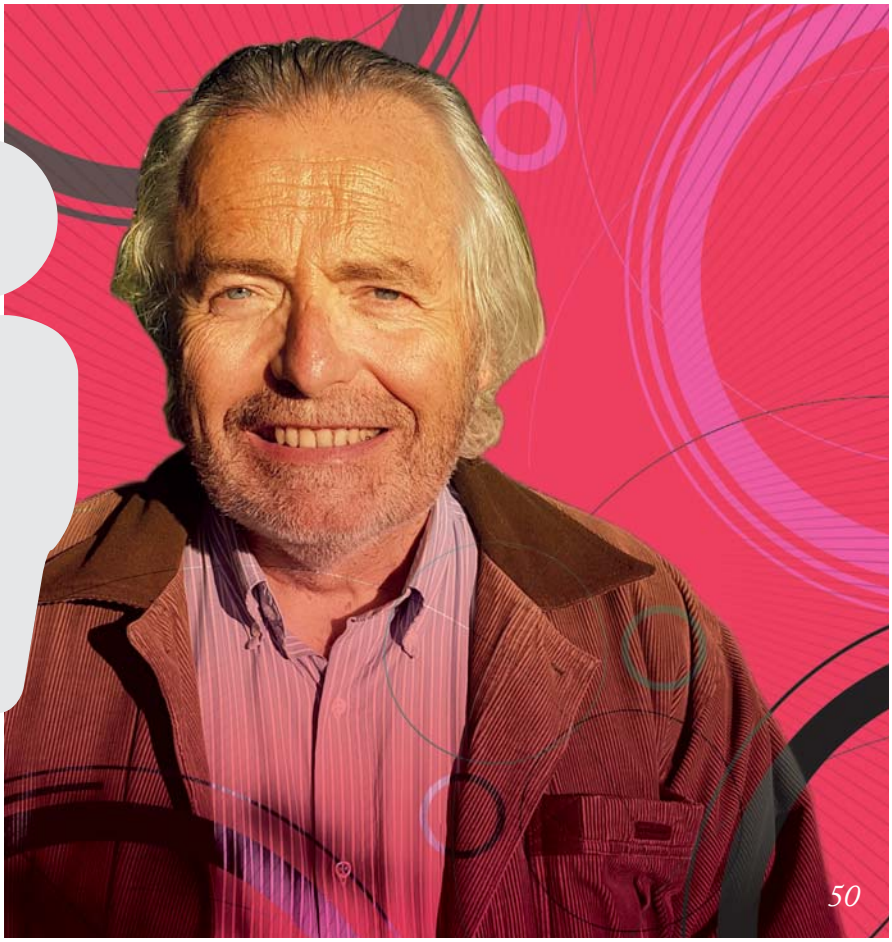


On The Cover

Revving up for the fourth industrial revolution



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Stronger Together

A repurposed drug could help improve response rates to immunotherapies

Anti-fibrotic drug Setanaxib may have found a new lease of life by boosting immunotherapy response rates, according to research published by scientists at the University of Southampton, UK (1). In recent years, there has been a resurgence of interest in immunotherapies, but approximately 80 percent of patients fail to respond.

The research group, led by Gareth Thomas, demonstrated that the drug helped improve immunotherapy response rates in mice by targeting cancer-associated fibroblasts (CAFs) – cells that Thomas' previous work had shown help tumors evade immune recognition, increasing the risk of a poor response to immunotherapy.

"We found that several cancer types were rich in CAFs but also contained low levels of T cells. By targeting NOX4 – an enzyme on CAFs, we realized that we could eradicate them from tumors," explains Thomas.

The group's findings led to a collaboration with Genkyotex in Geneva, who had developed Setanaxib, a NOX4/1 inhibitor, for the treatment of organ fibrosis and taken it through phase II trials. The drug was shown to prevent and reverse CAF formation, allowing anti-PD1 and vaccine-based immunotherapies to work more effectively in resistant tumors. Setanaxib has already undergone phase II clinical testing and is safe in humans. "Setanaxib's excellent safety profile means that we can begin to plan clinical trials in humans," Thomas explains.

And though clinical trials may be an immediate goal, the British team still intends to further investigate the regulation of CAF differentiation and function to develop new cancer therapies. "CAF remains a relatively poorly characterized cell population, and so we have adopted new technologies, including single-cell gene sequencing, to identify novel CAF subgroups in cancers," says Thomas. "Intriguingly, we have discovered several different types of CAF that likely have different functions. We have been investigating the mechanisms regulating their accumulation and distribution in tumors, and how they interact with other cell types. In this way we hope to get a better understanding of how the tumor microenvironment makes cancers more aggressive."

The project was funded by Cancer Research UK. The charity is also funding the group's ongoing study examining strategies for combining anti-cancer vaccinations with CAF-targeting in triple-negative breast cancer.

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INFOGRAPHIC

Culling Counterfeits

What headway has been made in the fight against fakes?

1 in 10

medical products in developing countries are fake or substandard

The unlicensed and fake medicines trade is worth **€4 billion**

China and India are considered large sources of counterfeit drugs

Counterfeits can be attributed to **116,000 deaths** in sub-Saharan Africa each year

COVID-19 IN BRIEF

Emergency authorizations, new partnerships, and price hikes… What's new in business?

- The FDA has granted Gilead emergency use authorization for remdesivir. The drug is still undergoing clinical trials but the authorization will allow it to be used in patients hospitalized with symptoms of COVID-19. "From day one, the FDA has been committed to expediting the development and availability of potential COVID-19 treatments. Today's action is an important step in our efforts to collaborate with innovators and researchers to provide sick patients timely access to new therapies where appropriate, while at the same time supporting research to further evaluate whether they are safe and effective," said Stephen M. Hahn, the agency's Commissioner, in a statement.
- Moderna Therapeutics has struck a deal with Lonza to manufacture its COVID-19 vaccine candidate, mRNA-1273. As part of the ten-year collaboration, Lonza will set up manufacturing suites within its facilities for the ramped up production of the new vaccine, as well as other products developed by Moderna. mRNA-1273 is currently being investigated in a Phase I clinical trial.
- A survey published by the Association for Accessible Medicines shows that, on average, the cost of shipping generic medicines has increased by 224 percent amid the COVID-19 pandemic. As the demand for certain drugs has increased during the pandemic, a number of factors have made it increasingly difficult for companies to supply them. According to the AAM, the massive price hike can be attributed to reduced international transport; government-enforced work from home orders, and trade restrictions.

Editing for Purity

Secretome engineering eliminates unwanted proteins in CHO-based bioprocessing

When CHO cells are used to produce recombinant-protein drugs, they can also produce many other unwanted proteins. Although these are removed during purification, they add to manufacturing costs and reduce efficiency. Researchers at the University of California, San Diego, and the Technical University of Denmark have published a paper showing how they used "multiplex secretome engineering" to increase recombinant protein production and purity (1).

The work builds on prior computational work showing that a relatively small number of unwanted proteins account for the majority of cell energy and resources (1). This inspired the researchers to eliminate the dominant contaminating proteins to free up cellular resources.

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Operation Pangea

In 90 countries, Interpol's Operation Pangea: made **121 arrests** seized **4.4 million** units of illicit drugs to the value of **€13 million and dismantled 37** organized crime groups

Operation Pangea also found:

2000 online advertisements related to COVID-19

Over 34,000 unlicensed and fake products advertised as:
Corona spray
Corona packages
Coronavirus medicine

Sources: OECD and EUIPO, "Trade in Counterfeit Pharmaceutical Products", (2020). Available at: https://bit.ly/2S3y4gD
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Better Use Case

How immunotherapy could be used to treat infectious diseases

Though TCR therapies are typically associated with treating cancer, researchers from Duke-NUS Medical School believe they could offer therapeutic value in various infectious diseases, including hepatitis B (HBV), HIV, and COVID-19 (1).

"There is more definitive data showing that virus-specific CD8 T cells (white blood cells that kill damaged cells) are important for the control of viral infections than solid cancers. But most cell therapies target tumors," says Antonio Bertoletti, a professor at Duke-NUS Medical School. "This pushed us to investigate whether similar results could be achieved in HBV and COVID-19."

The team has already demonstrated how TCR T cells target SARS, and now aim to investigate how the same therapeutic methodology could be applied to SARS-CoV- 2 (COVID-19). They also plan to investigate the role of different components of the immune system in the control of SARS-CoV-2.

"We need to understand whether antibodies or T cells are more important for control of infectious disease," says Bertoletti. "Developing a better understanding of these factors will be crucial to design effective treatment strategies."

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Alleviating the Pressure

Gene therapy shows promise for glaucoma in a mouse model

Researchers from the University of Bristol, UK, have used gene therapy to tackle glaucoma – a common cause of blindness and a disease with no cure. In an attempt to lower intraocular pressure (IOP) – a common mode of intervention – the researchers used a single intravitreal injection to deliver gene therapy that reduced the production of aqueous humor in the eye (by disrupting Aquaporin 1). In turn, the lowered pressure prevented damage and, importantly, preserved nerve cells in the induced mouse model of ocular hypertension (1).

"Though most patients use daily eye drops, these have side effects," explains Colin Chu, a research fellow at the university. "Glaucoma surgery is also available but it requires skilled surgeons, intensive follow up, and often fails over time."

According to the researchers, the approach, which combines CRISPR-Cas9 with viral gene vector technology, has the potential to provide long-lasting IOP reduction with a single injection – and that could help alleviate the treatment burden for patients and clinicians alike.

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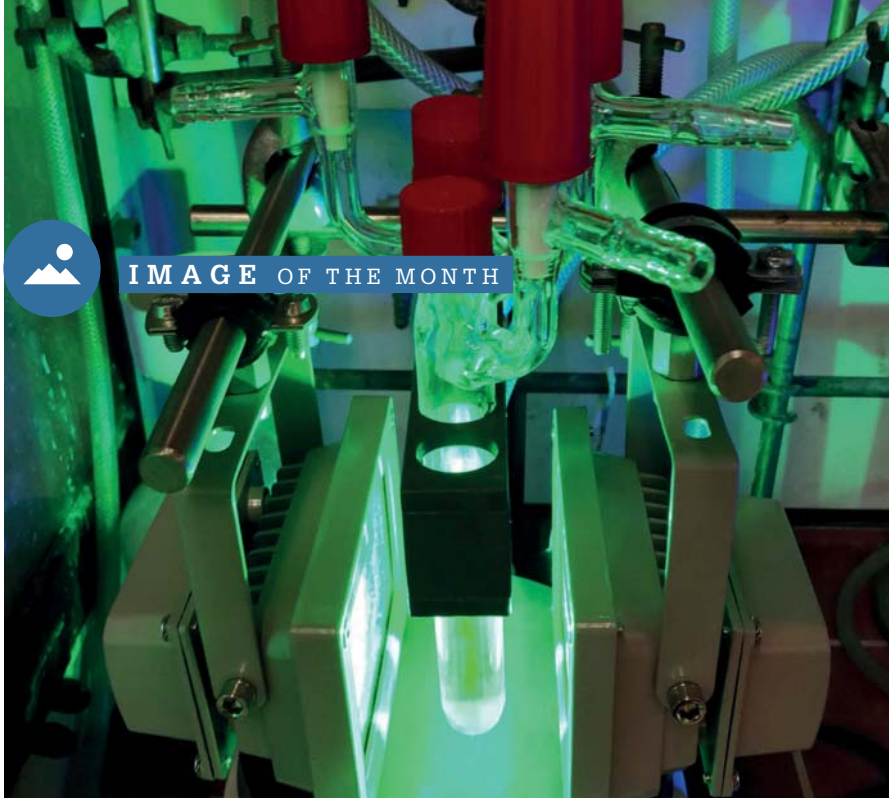


IMAGE OF THE MONTH

Let There Be Light

A light-emitting titanium catalyst could serve as a cheaper and safer alternative to commonly used toxic metals, such as ruthenium and iridium, during the production of antiviral medicines. *Find out more at https://bit.ly/2XWdZwk* Credit: Zhenhua Zhang

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

QUOTE of the month

"Viral vector manufacturing has transitioned from a niche industry to the cornerstone of the future of biopharmaceuticals, but few companies have the scale and quality systems in place for the commercial manufacture of these products."

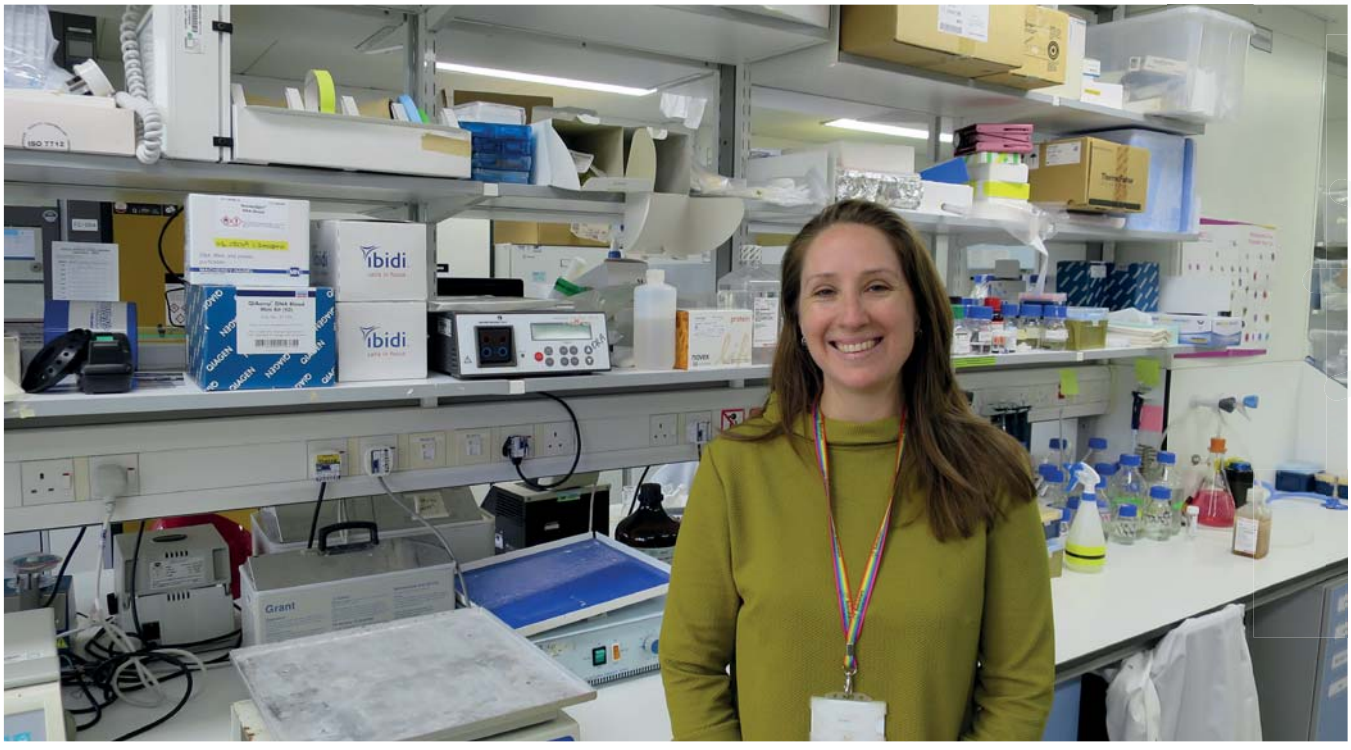
Udit Batra, a member of the Merck Executive Board and CEO of the Life Science business, on the company's plans to invest in a new commercial manufacturing facility for viral and gene therapies. Read more at https://bit.ly/353jNpC

Winning Innovation

Announcing the grand winner of The Medicine Maker 2019 Innovation Awards

In December 2019, we published The Medicine Maker 2019 Innovation Awards, showcasing the top 16 drug development and manufacturing technologies to hit the market during 2019. But which technology was truly the best? We asked you, our readers, to decide in a public vote on The Medicine Maker website. After counting the votes, we can finally reveal the grand winner: the KUBio Box for Viral Vectors, produced by Cytiva (formerly GE Healthcare). The modular platform provides rapid access to viral vector manufacturing capacity and supports manufacturing scale up to 200 L.

Close behind the KUBio Box for Viral Vectors were two runners up: Everic – modular vials suitable for high potency drugs – from Schott, and StarTab – a starch-based excipient for direct compression – from Colorcon.



Back to Immunity

Can we reverse the effect of the ageing process on the immune system?

As we age, our immune system function declines. Older people are not only more susceptible to serious infections, they are also less able to benefit from protective vaccines. A team led by Michelle Linterman, a group leader of the Babraham Institute immunology research program, is working to understand why vaccination tends not to work well in older individuals – and if there is a way of reversing the age-related decline of the immune system.

In any vaccine development, Linterman says it is important to enhance the germinal center reaction, which depends on interactions between multiple cell types. She theorized that defects in these cells could explain poor immune response.

In their latest work, the researchers show how an existing drug, imiquimod (incidentally, a cream for genital warts), was repurposed to help boost immune response in mice (1). "Our research showed that older mice and humans produce less of the cytokine Type I interferon upon vaccination," Linterman explains. "Imiquimod is a known stimulator of Type I interferon, and its cream formulation allowed it to be applied directly over the vaccination site. In mice, we were able to boost the number of stimulatory cells, and restore the formation of T follicular helper cells and dendritic cells."

The work could point the way towards overcoming some of the impact that age has on the immune system. Previous work by Linterman has also shown that the germinal center response in the gut of aged mice could also be boosted – and even increased above that of young mice – through the use of fecal microbial transplantation (2); however, the team has yet to investigate this approach in the context of vaccine responses. Given the number of approved medicines on the market, Linterman says there are a "plethora of options" for further repurposing.

"Our research has been five years in the making, but the COVID-19 pandemic has highlighted how important it is to ensure that any vaccine that is developed works well in older people," said Linterman. "We are planning to test potential candidates in aged mice to determine whether they stimulate a robust immune response in the context of this preclinical model of aging."

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Tracking the Pandemic

A clinical trial tracker aims to encourage international collaboration on COVID-19

"COVID-19 has created extreme uncertainties – a dearth of historical information combined with the need for safety, statistical rigor, and speed has prompted the rapid surge in published clinical research," says Edward Mills, Vice President of Real-World Evidence and Senior Principal Scientist at Cytel, a statistical software developer.

But the volume of new data being produced presents a significant problem: information is scattered across multiple platforms, making it challenging to comparatively measure treatment effects across trials. Attempting to pull this data into one platform, Cytel – in collaboration with the Bill and Melinda Gates Foundation – has created a global, open-access COVID-19 clinical trial tracker.

Mills hopes the tracker's live dashboard will encourage more international cooperation; scientists and other stakeholders can find the most up-to-date information on registered trials in one place, and reach out to researchers who have already made some headway. "As more results begin to come in, our data scientists will curate information from different trials to provide insights regarding various patient subpopulations. This should also help our international research community to avoid duplicating studies," Mills adds.

Initially, the company asked their partners to supply them with data, but they have now tapped into trial registries in several countries. As new trials begin, they are added to the tracker. Companies who want to share their trial designs or results can also do so through submissions directly on the website.

According to Mills, the rapid launch of the platform can be put down to the international level of collaboration the pandemic has inspired. "There has been a substantial increase in cooperation among industries and countries normally competing with each other. It is fascinating, as a scientist, to see so many great minds working through a variety of difficult challenges to achieve the same objective."

The COVID-19 Clinical Trials Tracker can be accessed at www.covid19-trials.com

In My View

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

The Pandemic Diaries

We asked medicine makers around the world to tell us how their professional and personal lives have changed during the ongoing COVID-19 crisis

Adrian Wildfire, Scientific Director at SGS

Would you like to share your view on how COVID-19 has changed the pharma industry – and the world as we know it? Email stephanie.sutton@texerepublishing.com

The COVID-19 crisis is prompting the vaccine industry to find new ways of accelerating research and development, and we're also seeing regulators taking unprecedented steps to help us. I was interested to note recent guidelines from a virtual workshop on COVID-19, convened by the FDA and EMA, involving global representatives. Although the meeting acknowledged the theoretical risks of vaccine-induced disease enhancement, which would need to be addressed during first-in-human trials, they also agreed upon a number of pathways to licensure and gave practical suggestions, including a decreased emphasis on efficacy and safety studies for proven platforms: "It is not required to demonstrate the efficacy of the SARS-CoV-2 vaccine candidate in animal challenge models prior to proceeding to FIH clinical trials" (https://bit.ly/2VulWr9).

"The industry and its regulators are proactively working to identify and progress novel solutions, but we need to ensure that this focus is maintained."

The regulators are also looking at how they can reduce legislative burden and actively progress drug and vaccine candidates into the clinic. The FDA has set up the Coronavirus Treatment Acceleration Program, with the stated aim to: "use(s) every available method to move new treatments to patients as quickly as possible, while at the same time finding out whether they are helpful or harmful" (https://bit.ly/3eIH3xq). Additionally, the EMA has waived fees for scientific advice for COVID-19 related drugs and vaccines, and is ready to review any applications for marketing authorization within the "shortest possible timelines."

The industry and its regulators are proactively working to identify and progress novel solutions, but we need to ensure that this focus is maintained – even following the end of the current COVID-19 pandemic – because coronaviruses will not be the last threat to mankind. Overpopulation, globalization, and unrestricted international travel will mean that future pandemics could see a faster spread with much higher mortality, including children. In my view, I think we should listen to CEPI's advice: "[...] we should continue developing the most promising (vaccine) candidates to a point at which they can be stockpiled and ready for trials and emergency authorization should an outbreak recur. A global financing system that supports end-to-end development [...] will be a critical component of future pandemic preparedness."

Andy Lane, Commercial Director at The Native Antigen Company

I remember when reports of a novel coronavirus first began to emerge in late December. Somebody mentioned it at the weekly product development meeting – more as a curiosity than anything else.

However, it soon became apparent that the new coronavirus was something serious for us to contend with. Within days, the outbreak in Wuhan ballooned to hundreds of cases, turning heads in academia and industry, alike. Wild speculation followed. Were we on the verge of a global pandemic? Was this the next Disease X?

As cases continued to mount, there was little we could do but sit and wait. R&D were desperate to start their projects, but with no gene sequence, there was nothing to work with. Then, in early January one of our scientists stumbled across a draft genome on a virology blog. From there, it was all systems go. R&D set to work designing the plasmids, transfecting the cell lines and exactly one month since the genome was published, we released S1 and S2 subunits of the SARS-CoV-2 Spike protein.

"Within days, the outbreak in Wuhan ballooned to hundreds of cases, turning heads in academia and industry alike."

For me, it's a strange feeling as I drive through the sleepy Oxfordshire countryside in the morning. Lockdown has made it feel like the world is on pause. Yet, I step in the lab and it's never been busier. The team remains hard at work and we are now scaling antigen manufacturing capabilities to support more researchers in developing diagnostics and vaccines against COVID-19, which will be vital in stemming the spread of this disease.

Mike Grippo, Senior Vice President, Strategy & Corporate Development at Catalent Pharma Solutions

COVID-19 is one of the greatest humanitarian challenges of our lifetime. I see companies acting with great resolve and resilience, addressing the immediate challenges of COVID-19, and what it represents to their workforce, customers, partners and patients. I see "unsung" heroes – people who persevere and perform in important but less visible jobs – making a significant difference. It makes me proud to be part of Catalent and proud to work in the biopharma industry. My hope is that when we emerge from this crisis, we will reimagine and reinvent. Necessity is the mother of invention. Our industry is trying new things every day. What have we learned that can be applied to the future and perhaps made permanent? How can we accomplish things faster, more efficiently, and at lower cost? What did we stop doing that is not missed? Perhaps we can apply these learnings to the drug development process. I see a period emerging where governments are going to focus on decreasing the time and cost to get new drugs to market. We are already starting to see great cooperation between our industry and global regulatory bodies around COVID-19 trials. Hopefully, much of this collaboration will extend into other lifesaving and life-preserving therapeutic categories.

"We are already starting to see great cooperation between our industry and global regulatory bodies around COVID-19 trials."

Viral Vectors in Vogue

We must collaborate to address stability challenges in viral vector manufacturing

By Arvind Srivastava, Technical Fellow at Avantor

Rapid advances in cell and gene therapy development have led to new approvals, but commercialization has introduced a whole raft of new challenges. How do we produce these therapies safely, cost-effectively, and in time to meet growing global health needs? Stable, safe workflows for viral vector processes are critical; after all, the vector is the delivery mechanism for the therapy. The vector manufacturing process includes vector amplification, expansion and purification steps, followed by fill and finish.

Over time, vectors may undergo undesirable changes, such as aggregation, unfolding, surface absorption, oxidation and deamidation during storage, shipping and handling, which can cause the vector to fail in properly delivering the therapeutic (1, 2). Manufacturers – and the companies that supply critical raw materials to them – must examine how viral vector stability can be affected, and then consider how to solve these challenges to ultimately improve the end product delivered to the patient.

Vectors can cross-link through host cell proteins and DNA on the viral surface, forming aggregates that can cause the vectors to lose therapeutic efficacy and lead to unwanted immune response (2). Aggregates can also increase the viscosity of the vector solution, making it more difficult to load the vector into syringes and inject the material (3). Aggregation can be addressed with an endonuclease treatment, used to minimize the host cell proteins and DNA-mediated vector aggregates during downstream manufacturing processes (2), or with excipients added to processing steps to reduce viscosity (4).

Vectors can also lose the ability to perform their primary function in cell and gene therapy treatment: delivering the therapeutic load to the target cells in the patient. This vector stability challenge has been shown to be related to environmental conditions. For example, viral vectors stored in PBS formulations and held at room temperature for three days were 50 percent less efficient in delivering a therapeutic payload (1). High purity sugars and PEG for vector formulations are materials now offered by many excipient manufacturers (5), which can also be used to combat efficacy challenges (1). Refrigeration can also help solve aggregation and infectivity loss challenges. In another study, the stability of an investigational product was reported to be significantly better at -70 °C than -20 °C and 5 °C (2). Another environmental issue to consider is how vectors can oxidize upon exposure to light or due to metal ion impurities in the raw materials and excipients used to manufacture the viral vector (3). Methionine has shown to significantly reduce the infectivity loss in an adeno-associated virus 5 when stored at 37 °C (3). Infectivity can also be reduced by the presence of free-radical scavenger supplements (6).

Viral vector manufacturers, if they are not already closely managing pH levels, need to pay attention, as the pH and ionic strength of vector formulations can also impact vector stability and infectivity. For example, the infectivity study of adenovirus type 5 at 15 °C demonstrated its lowest infectivity loss between pH 6.0 and 7.6 (6). Other studies have demonstrated effectiveness of salts; for example, >200 mM of a salt, such as magnesium sulfate, sodium citrate, sodium chloride, sodium phosphate or sodium sulfate was shown to significantly reduce vector aggregation in one study (2). The study further shows that a multivalent salt, like magnesium sulfate, was even more efficient than a monovalent salt, such as sodium chloride (2).

Conditions within formulations can also cause instability in viral vectors. Vectors can unfold, aggregate or even precipitate upon shear stress. A study was conducted to assess AAV2 vector recovery in the presence and absence of a nonionic surfactant. The vector was diluted from the concentrated stock solution and placed into a PBS buffer with and without the nonionic surfactant, and then passed through three different injection devices. Vector recovery was significantly higher in all three devices when the formulation used a surfactant (2). These results suggest that surfactants are required to protect vectors during manufacturing, storage and shipping.

The challenges that viral vector manufacturers encounter today are similar to the ones monoclonal antibody manufacturers experienced two to three decades ago. Drug manufacturers and chemical and excipient suppliers worked together to standardize the process for monoclonal antibodies – and now they have the opportunity once again to demonstrate the importance of partnerships. The need to develop innovative materials solutions for cell and gene therapy products is clear.

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Tackling Off-Target Effects

CAR T therapies are seeing fantastic results. Now let's find a way to make them safer

By Nicola McCarthy, Screening Business Unit Manager at Horizon Discovery, UK

In CAR T therapy, T cells are genetically modified to express a chimeric antigen receptor (CAR) that recognizes, binds and destroys specific tumor antigens. The approach has huge potential in oncology, particularly for blood cancers. To date, however, CAR T therapies have had limited clinical success, with only two therapies approved: Novartis' Kymriah for B-cell acute lymphoblastic leukemia (ALL), and Gilead's Yescarta for large B-cell lymphoma. Both have demonstrated impressive results, but they are also expensive and can come with serious side effects due to inflammatory responses from patients.

There are two different types of CAR T therapy. Autologous therapies use a patient's own immune cells as the source to produce CAR T cells, but are labor intensive and costly to manufacture. Allogeneic, or "off-the-shelf therapies" use an external source to produce CAR T cells for many patients, which allows the cells to be manufactured at scale and stored until needed. Implanted allogeneic cells, however, may be recognized as foreign and rejected by the patient's immune system. Worse still, the implanted cells can reject the host in a complication known as graft versus host disease (GvHD). GvHD is largely a result of T cell receptor molecules on the surface of the implanted CAR T cells that reject host tissue. In addition, both autologous and allogeneic therapies are susceptible to a phenomenon known as T cell fratricide, where the cells attack and kill each other. This lowers the number of active CAR T cells in a therapeutic dose and has a detrimental effect on T cell expansion and tumor-killing capabilities.

One approach to improve the safety and efficacy of CAR T therapies is to prevent the expression of genes that cause unwanted immune responses. This can be achieved in a number of ways, including harnessing gene editing technologies (e.g., CRISPR) and gene silencing methods, such as RNA interference (RNAi).

In the latter, gene silencing is achieved through degradation of target mRNA molecules that prevent the production of functional proteins. This method can be improved by using short hairpin RNA (shRNA), an artificial RNA molecule that contains a short hairpin sequence encoded within a DNA vector. After the shRNA is delivered to the cells, it mimics the endogenous RNAi pathway to achieve prolonged gene silencing.

In my view, gene silencing via shRNA is a more promising path to improving cell therapies than gene editing techniques because the shRNA molecule can be introduced in the same vector as the CAR construct. In contrast, modifying CAR T cells with CRISPR is much more complex as it requires the delivery of Cas protein and guide RNA.

Although both CRISPR and shRNA methods can exhibit off-target effects, shRNA off-target effects are well characterized and can be limited by using a microRNA-adapted scaffold to increase the relative potency of the active strand over the passenger strand.

There are currently over 800 CAR T trials in the clinic, illustrating the continuing faith within the life sciences industry of the potential for CAR T therapies to transform cancer treatment. The issues holding the field back largely stem from unwanted immune responses, which can be tackled by targeting the gene expression of relevant proteins. The simplicity and manageability of shRNA gene silencing makes it an attractive alternative to gene editing approaches, and has been used a numwber of times to improve the safety and efficacy of cell therapies. For example, in a collaboration between Horizon Discovery and Celyad, gene-silencing shRNA molecules have been incorporated into Celyad's existing CAR T candidates, using the SMARTvector shRNA platform. The two companies are working to limit GvHD in allogeneic therapies and reduce T cell fratricide in autologous therapies.

This is only one amongst a number of approaches being trialled. In time, I believe we will achieve the ultimate goal of delivering safe and effective "off-the-shelf" CAR T therapies, and changing the face of cancer treatment.


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REVVING UP FOR THE REVOLUTION: INDUSTRY 4.0

WE'RE MOVING TOWARDS A DATA-DRIVEN FUTURE OF ENHANCED MANUFACTURING. AND WE MUST LAY THE FOUNDATIONS TODAY.

By Gareth Jenkins, Chief Scientific Officer at Arcinova

Over the span of my career, I've always been interested in how advances in science and technology can help us to reinvent approaches to pharmaceutical development – and how we can use those advantages to increase speed and efficiency. In essence, we must always look to how we can harness the latest technology and process innovations to improve what we're doing. The comprehensive approach to continuous improvement through automation and data-exchange spans many industries, and is generally known as "Industry 4.0". Before joining Arcinova as CSO and leading its innovation and technology strategy, I was the CEO for Britest, a process understanding consultancy business. Back then, a major project for us was a government-funded initiative called ADDOPT, which stands for Advanced Digital Design of Pharmaceutical Therapies. The goal was to examine what was happening as the Industry 4.0 concept took root (including emerging buzzwords and challenges) in other manufacturing industries, and to ask what types of projects would demonstrate the power of the approach. We were also tasked with asking whether it was worthwhile for pharma development and manufacture. (And to cut to the chase: yes, I believe there is considerable and wide-ranging potential value for pharma!)

ORIGINS OF INDUSTRY 4.0

As a shorthand term, Industry 4.0 means that we are in the early stages of a fourth industrial revolution. For me, this new paradigm is all about innovation in manufacturing. Where it will take us is not yet fully clear, but how we got here is a function of revolutions one through three.

The first industrial revolution in the 18th century, Industry 1.0, was marked by the switch from manually operated machinery to steam-powered industrial machines. It started with looms in the textile industry before spreading elsewhere. It took approximately 70 years, but it completely revolutionized manufacturing by replacing the physical power of human workers with vastly more powerful and efficient machines.

The second industrial revolution, Industry 2.0, occurred around 1870 to 1920, and was characterized by replacing steam with electricity. At the time, pioneers who were interested in applying the new technology had to first generate their own electricity. There was no power grid; you had to build your own power station, and you had to think long and hard about how to invest in it. There's a historical echo with Industry 4.0 here – both paradigms are about tapping into new resources, and then figuring out if they can be accessed as commodity utilities, or if you'll need to generate the building blocks in-house before you can reap the advantages.

Beginning in the early 1970s, the third industrial revolution, Industry 3.0, saw the addition of digital technology to monitor and control the function of electrical machinery. The goal became to make production even more efficient and safe using computers, sensors and robotics – the dawn of automation.

The current change – from the third to the fourth industrial revolution – is marked by a move toward a consolidated, full-spectrum, data-driven approach to design and manufacturing. It takes advantage of increasingly powerful digital tools to control and inform the automated process to optimize outcomes. In short, factories are becoming smarter.

THE POWER OF CONNECTIONS

Not that long ago, cars had analogue fuel gauges with an indicator needle that moved between full and empty. These gauges were somewhat imprecise – and when the indicator was in the red you were taking a gamble! But they were useful as a rough indicator of your remaining fuel. About 20 years ago, manufacturers began installing digital sensors inside of fuel tanks. These sensors can be calibrated to show the number of liters or gallons remaining in your tank, providing a more precise measure. Car makers also started to install sensors that monitor fuel efficiency. By combining the two pieces of information, the remaining volume of fuel could be translated into the number of miles you can drive before you're running on empty. The result – car or fuel range – is really a (late) example of an Industry 3.0 transformation, and provided a more useful context-based and quantitative measure for the driver.

An example of Industry 4.0 would be a system that predicts early on when the car's fuel will run out, and makes plans to avoid the issue – for example, a car that automatically offers

"AS A SHORTHAND TERM, INDUSTRY 4.0 MEANS THAT WE ARE IN THE EARLY STAGES OF A FOURTH INDUSTRIAL REVOLUTION."

a list of open gas stations within the remaining driving range from your location, plotting a route to the one selected. The same principle can be applied to Industry 4.0 in pharma, where "self-aware" equipment components can report on their condition, indicate when maintenance is due, and report on their predicted lifetime. The savings that could be made using this capability are great indeed.

It is this combination of different data sources and control systems that creates new possibilities for better products. Another example within Pharma 4.0 is the development of smart epichlorohydrin auto-injector pens for emergency treatment of anaphylactic shock. These are fitted with sensors that monitor temperature, location and use. They can alert the user when the pen is close to its expiry date or has been exposed to extremes of temperature. More importantly, when the auto-injector is used, it can send a notification, including its location, to a circle of contacts and a pharmacy chain. This triggers the allocation of a replacement auto-injector at the nearest pharmacy for pick up or delivery to the patient within a few hours.

"IT IS THIS COMBINATION OF DIFFERENT DATA SOURCES AND CONTROL SYSTEMS THAT CREATES NEW POSSIBILITIES FOR BETTER PRODUCTS."

The latter example highlights the potential to gather data from patients and use it to create a feedback loop in the supply chain that allows manufacturers to adjust to changing demand more rapidly – perhaps avoiding the manufacture of drug batches that would remain unused. What if we could drive demand the other way, so that manufacture is perfectly matched to patient demand? The industry wouldn't need drugs that remain stable for five years because we could use a just-in-time manufacturing approach.

A just-in-time approach could be particularly beneficial for clinical supply. One problem with early-phase clinical trials is the unpredictable time it takes to recruit patients. If you're dealing with a rare disease, for example, there simply aren't that many patients available, and it's difficult to predict how many you'll get over a set time period. If your two-year clinical trial requires 200 patients, ideally, you'd enroll them at a rate of around 10 patients per week for six months. But what if you recruit one or two in the first month, then none for a month or two, and then another 20 in the same week? It definitely presents uncertainty for clinical supply – how much drug product should be manufactured and when? How do you respond if 30 new patients turn up and you've only planned for 10?

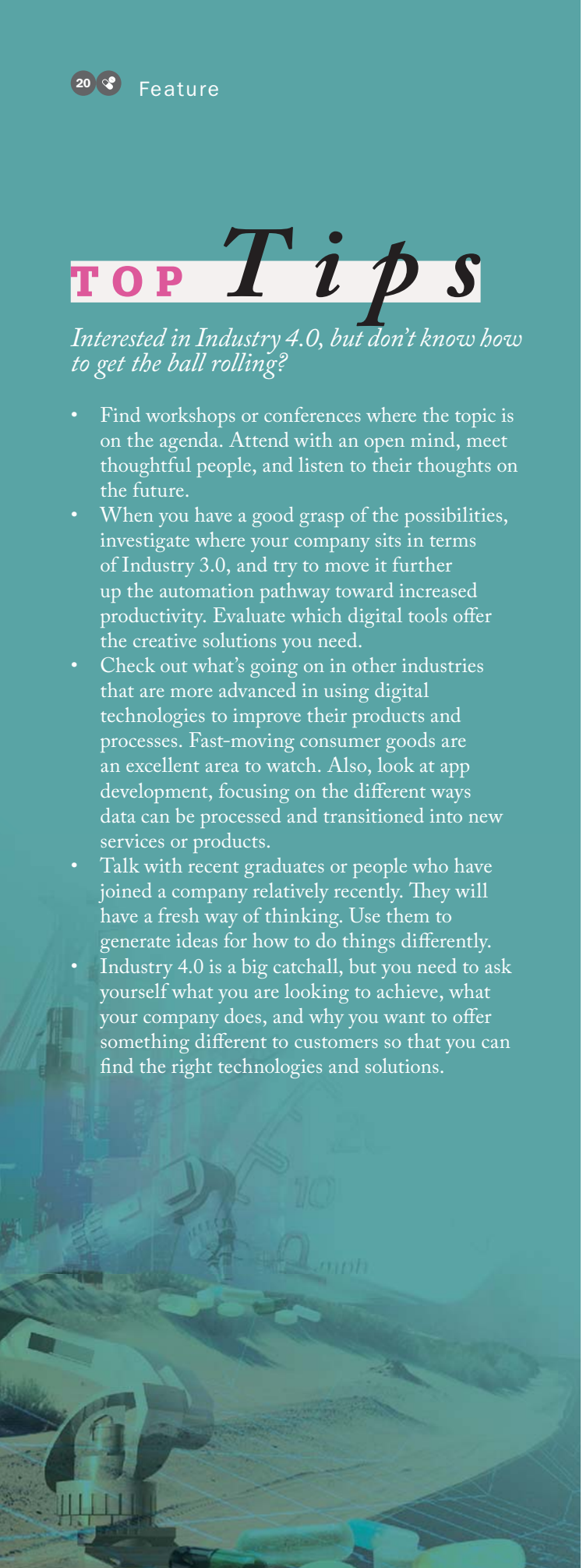
In the past, we've dealt with this uncertainty by producing an excess quantity of the drug, which we've put into storage in the hope that it doesn't exceed its shelf life by the time the last patient has been recruited for the study. Of course, this makes the whole process expensive and wasteful. Worse, if the first patients start to show adverse effects, you'll stop the clinical trial anyway. The material already produced will never see a patient – and that's when the quantities of money wasted across the clinical supply chain can begin to astound even a long in the tooth scientist like me...

What if, every time a patient arrives in the hospital with a certain diagnosis and meets the right criteria, they could be enrolled in a clinical trial – a process that, with the right systems and checks, could even be automated. At that point, the drug supply for that patient could be manufactured then and there, and delivered to the clinic for administration. Industry 4.0 offers the sort of technological infrastructure and design ethos that I believe can get us towards that goal. As a result of this new way of thinking and the technological advances supporting it, we're figuring out

TOP *Tips*

Interested in Industry 4.0, but don't know how to get the ball rolling?

- Find workshops or conferences where the topic is on the agenda. Attend with an open mind, meet thoughtful people, and listen to their thoughts on the future.
- When you have a good grasp of the possibilities, investigate where your company sits in terms of Industry 3.0, and try to move it further up the automation pathway toward increased productivity. Evaluate which digital tools offer the creative solutions you need.
- Check out what's going on in other industries that are more advanced in using digital technologies to improve their products and processes. Fast-moving consumer goods are an excellent area to watch. Also, look at app development, focusing on the different ways data can be processed and transitioned into new services or products.
- Talk with recent graduates or people who have joined a company relatively recently. They will have a fresh way of thinking. Use them to generate ideas for how to do things differently.
- Industry 4.0 is a big catchall, but you need to ask yourself what you are looking to achieve, what your company does, and why you want to offer something different to customers so that you can find the right technologies and solutions.



how to run shorter batches of clinical drug manufacture so they can have a shorter shelf life. We no longer need them to sit around for years, because we shorten the link between enrolling a patient and manufacturing the clinical product.

FORMULATION 4.0

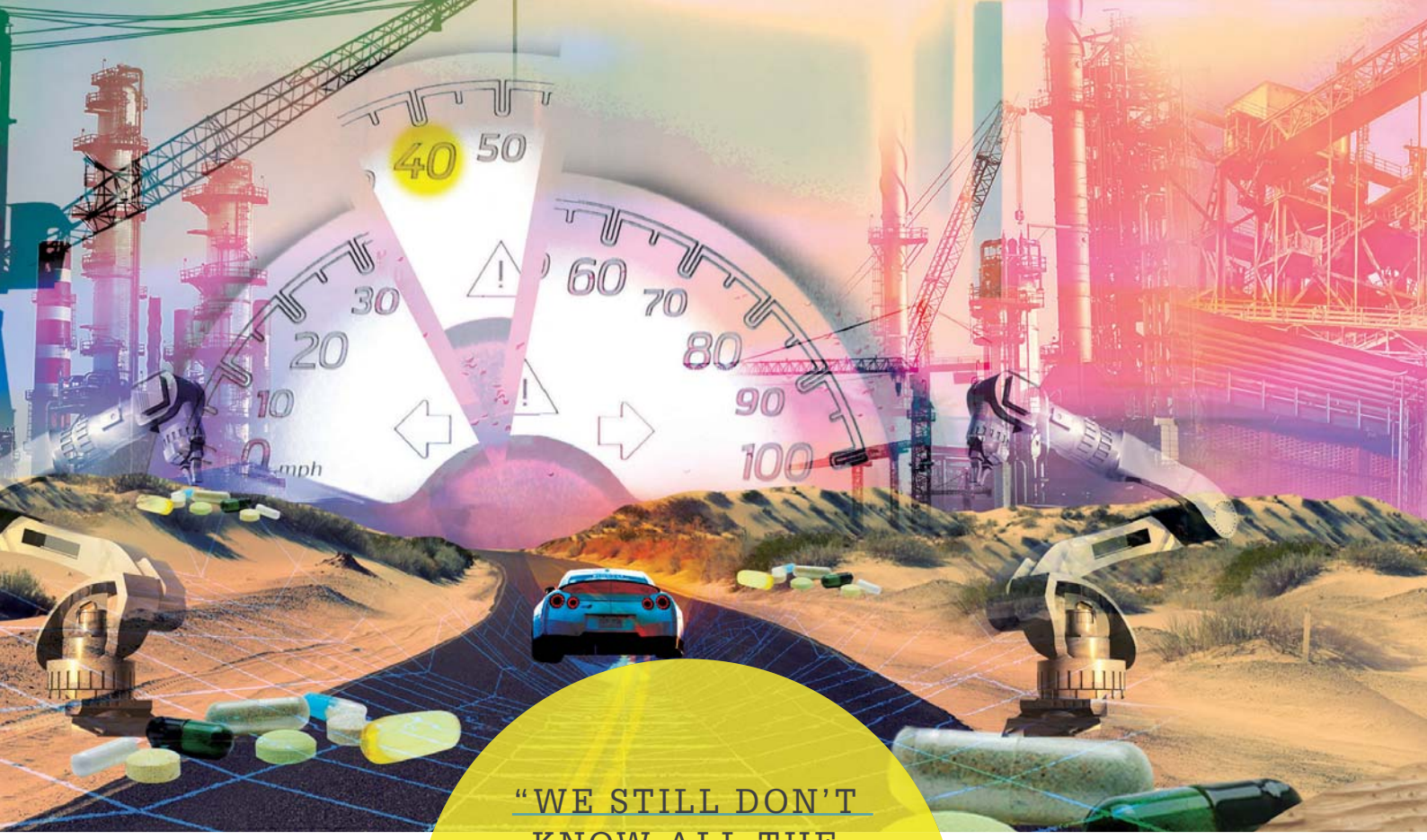
A data-driven approach can also be used to enhance formulation activity. The main challenges that drug developers face today with emerging drug molecules involve complexity, permeability and bioavailability. It's quite common to hear scientists describe an API as being like brick dust. Some of these APIs have incredible therapeutic potential – if we can figure out how to get them to the right part of the body at the right time, and in the right quantities. This problem is also multidimensional. You not only have to think about the atomic and molecular structure of the molecule, but also how it translates to its physical form when you get up to crystal size. After the crystals have been compacted together to form a tablet, there are still phenomena taking place on the molecular level. For example, if you make a very simple switch from a sodium salt to a potassium salt, you are not even changing a real bond, just the ionic association. But if you ask a physical organic chemist to predict what this will do to the tensile strength of the tablet? They won't have a clue.

Over the last 100 years, the pharma industry has formed countless drugs into tablets. If we captured all that "big data" and applied machine learning, important correlations could be found. And if we can get artificial intelligence to think about tensile strength and other manufacturability aspects, it would allow us to digitally design many different formulations. We can then design prototypes, and whittle down the choices to just a few to take into the physical world to gather hard data. The process would finetune the search for new APIs and remove redundant empirical experiments, which currently take up a lot of scientists' time.

LEARNING FROM EXPERIENCE

At Arcinova, we're plugging into some of these exciting areas and looking for opportunities in Industry 4.0 that can help us in our work. One area we are focusing on is using models to drive decisions and improve efficiencies – and we strongly encourage our process development chemists to adopt modelling as a component of any drug development process.

When we first start working on a molecule, we look to extract time-based data streams from every experiment we do. We don't just measure once every few hours; we set up



"WE STILL DON'T KNOW ALL THE WAYS IN WHICH TODAY'S TECHNOLOGY CAN AID DRUG DEVELOPMENT."

online analytical systems, pull the data constantly, and use it to really understand what's going on. From there, we can build a process model. Initially, it's always a simple fit-for-purpose process model to see how the process is behaving. We then use that process model to suggest where areas of failure might be, and we try to avoid them going forward, which allows us to be more efficient in process optimization and design. When we scale up the process, we can also create a digital model of the equipment first to see if we're likely to encounter any issues (for example, with heat transfer) or to identify aspects of a process that won't fit the standard equipment set-up. If the model highlights issues, chemical engineers can suggest solutions.

Collaborations can also help companies to find new opportunities for Industry 4.0. We are working on the Flowinova Project with the University of Nottingham, UK, which is primarily looking at how we can use continuous processing to perform certain chemistries at large scale. The Nottingham team is led by Prof. Sir Martyn Poliakoff and Prof. Michael George; they have performed substantial work in designing reactor systems that have a built-in feedback loop. They are also moving towards what I would call a self-optimizing reaction system, which is attached to a computer that monitors the outcome of each reaction and then modifies the input variables of the processes. For example, it may tweak the temperature, pressure or solvent concentration, and then run the experiment again. It continuously learns from the experimental data. You can leave it running overnight and the next day it can show you a picture of the process space it has hunted through, including where the reaction worked really well.

Ongoing work going at the University of Leeds, UK, has extended that one step further. At the moment, we tend to focus on optimizing just one factor like yield or conversion, but Richard Bourne is starting to look at what happens when you ask the computer to optimize based on different variables, such as yield, and how much waste the process conditions generate or how much of a scarce resource is needed – important factors for companies that want to focus on sustainability. You can only perform such multivariate optimization using machine learning-type algorithms. It is certainly too difficult for a human to do with a pencil or an excel spreadsheet. And this is why I'm so excited about Industry 4.0. It should help us do our jobs better.

MAKE THE DIFFERENCE

One key Industry 4.0 obstacle for pharma to overcome lies in the relative lack of interoperability among the technologies required to make the revolution happen. We need to be able to buy any piece of equipment, plug it into anyone else's piece of equipment, and then have it controlled by whatever process control system we happen to have invested in. On top of that, we need a smart layer over the top that can coordinate it all. Everything should work together seamlessly.

Right now, we don't have this. Each pharma company needs the flexibility to choose the best way of designing its processes, and the capability to buy technologies from a wide variety of sources. Currently, if the different systems won't speak to each other, it's up to clever folks in IT to write translation software to enable communication – like the early adopters of electricity who had to build their own power stations. But if we can remove all of that effort and expense with off-the-shelf interoperability, adoption will accelerate right across the field. At the moment, it is the early adopters – the people who can see ripening opportunities and are prepared to put in the research, time and labor – who are beginning to break down some of these barriers.

Revolutions are rarely easy. The move to Industry 4.0 will not be easy. There are many questions, and we still don't know all the ways in which today's technology can aid drug development and manufacturing. Today, there are countless different sensors and technologies that can pull different data streams together. If companies start using their imagination and trying new things, we can come up with solutions that were unthinkable just a handful of years ago. Remember that prior industrial revolutions took decades, so a true understanding of Industry 4.0 won't happen overnight. In fact, there are still a startlingly large number of chemical manufacturing plants that lack basic computer-automated process control. We need to work out how to get everyone on an even technological playing field before we can start to pursue some of the advanced digital approaches to harnessing 4.0 for pharma.

In the pharma industry, we all want to make a difference to patients. From the perspective of a contract developer, I want to help clients develop their drugs better and faster so they can treat unmet diseases, bring down manufacturing costs, and push forward advances in healthcare. We've embraced some aspects of Industry 4.0 and these have helped us transform our responsiveness to our customers. I would really like to see more pharma companies do something similar, and ultimately use these technologies to make medicines cheaper and more readily available. We are all patients, so we all stand to benefit from technology that expands our understanding of diseases, how to treat them, and how to manufacture therapeutics at a sustainable cost.

I hope to see you at the revolution – we have lots of work to do, but much to gain.

Gareth Jenkins is Chief Scientific Officer at Arcinova, UK

ROOM FOR *Optimization*

Richard Bourne's research group, located at the University of Leeds' Institute of Process Research and Development, focuses on the optimization of pharmaceutical processes using automated systems. Recently, he has been working on developing automated flow systems that combine online analysis, feedback control, and evolutionary algorithms that help with process understanding and optimization.

WHAT DOES YOUR WORK FOCUS ON?

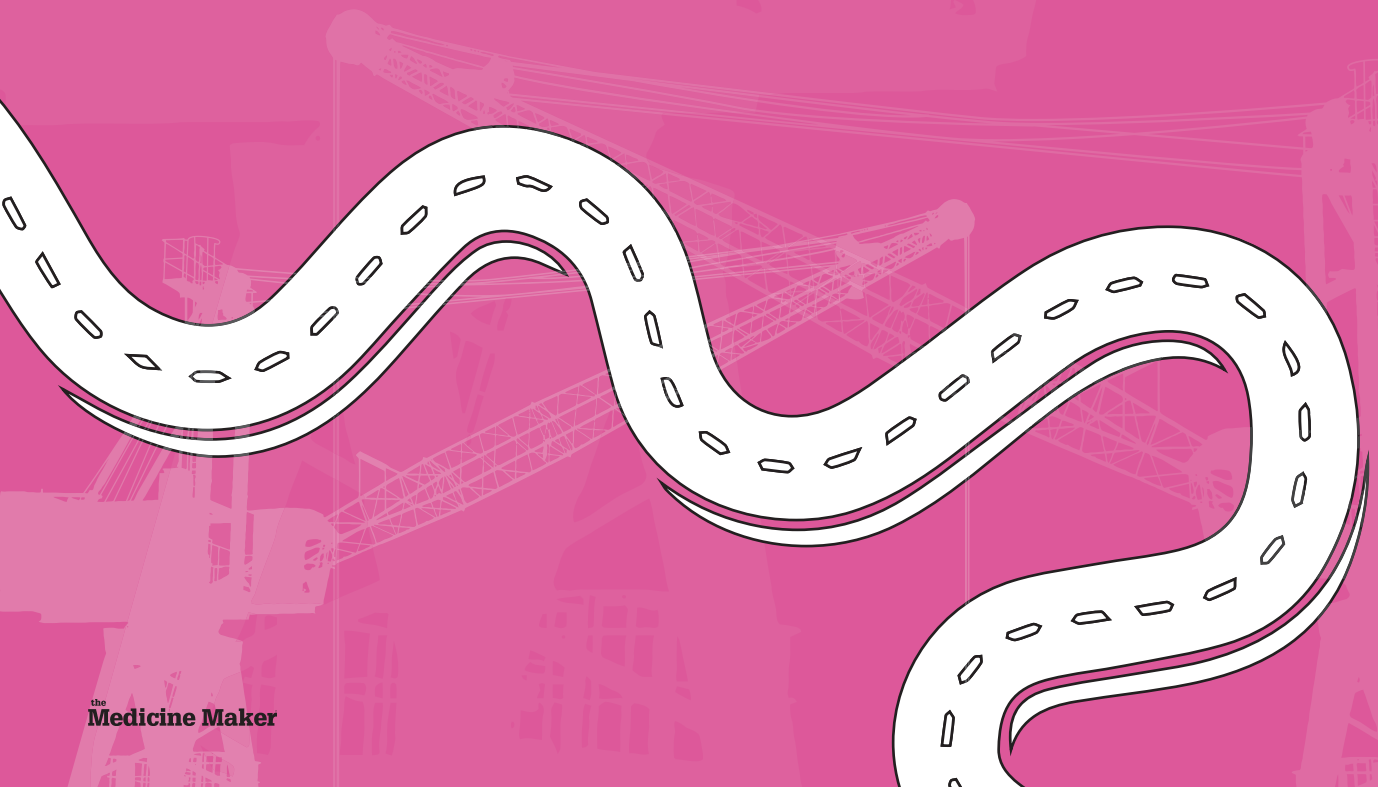
Continuous flow processes are more cost-effective than traditional production methods – and the pharmaceutical industry is becoming increasingly interested in their use. I've spent several years developing an automation platform that can help companies to more rapidly develop their processes. Pharmaceutical processes are fascinatingly complex, with many stages involved in the synthesis of therapeutics. I often work with innovator companies who generate new treatments, but face the pressures of limited development times due to patent lifetimes. Many companies also struggle with the challenges of clinical trials. Automated technologies can automate and optimize some processes, helping companies to more effectively develop their therapies.

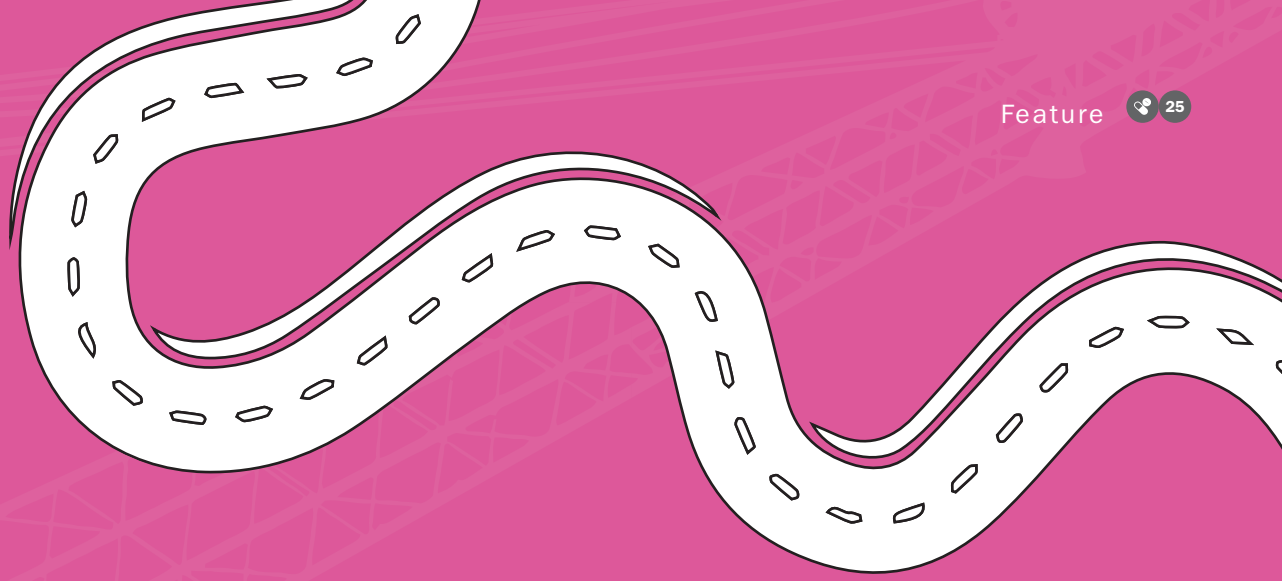
HOW DID YOU GET STARTED WORKING WITH ARCINOVA?

The collaboration followed a meeting with the Arcinova team at a Dial-A-Molecule Symposium in 2018. The Dial-A-Molecule network (https://bit.ly/2SrrmkF) was established by the UK's Engineering and Physical Sciences Research Council to "promote research aimed at a step change in our ability to deliver molecules quick and efficiently." It's an amazing initiative that has helped develop new links between academia and industry. Following this event, Gareth and the Arcinova team visited our facilities. Since then, we've been working together to develop new projects that integrate Industry 4.0 developments within their portfolio, such as implementing machine learning algorithms that help to optimize reactions. We are also working on developing our automation platforms to include other types of reactor including miniaturised systems such as continuous stirred tank reactors to broaden the scope of chemistry that can be studied with our Industry 4.0 approach.

AT WHAT STAGE IS THE WORK? WHAT ARE THE MAIN CHALLENGES RIGHT NOW?

The optimization platforms we've developed work very well for homogeneous chemistries with fixed chemical molecules – we can typically optimize new processes within a week, including a day of experimental time on the platform. However, it's a real





challenge to develop these automated platforms so that they can tackle heterogenous (solid/liquid) processes, but we hope to develop this in the future. We also need new algorithms and robotic systems to be able to change discrete parameters (such as solvents or catalysts) so we can find an optimal process with the optimized conditions.

WHAT ARE YOUR THOUGHTS ON THE FUTURE OF AUTOMATION AND INDUSTRY 4.0 IN PHARMA?

I think there are real opportunities in using new technology and Industry 4.0 approaches to transform how pharmaceutical processes are developed, but there are concerns that it may lead to a loss of synthetic chemists within the pharmaceutical industry. I believe that this is simply not the case. There will always remain challenging chemistries that cannot be performed by robots and we will also still require chemists to interpret the data generated and propose new experiments. The future will likely be chemists that are augmented with digital capability so that they can focus on the challenging work and automated platforms can perform the routine/laborious actions.

WHAT OTHER RESEARCH PROJECTS CONNECTED TO PHARMA ARE YOU INVOLVED WITH?

We collaborate with a number of companies, including AstraZeneca, GlaxoSmithKline, and Dr. Reddy's Laboratories. Examples include:

- Developing self-learning reactor systems for the automated development of kinetic models, with AstraZeneca. We're using mixed integer linear programming techniques, capable of kinetic model discrimination, to create an autonomous system that can evaluate and develop scalable process models.
- The Cognitive Chemical Manufacturing (CCM) EPSRC project. This project involves the University of Leeds, AstraZeneca, IBM, Swagelok, University College London, the University of Nottingham and Promethean Particles. We're developing an Industry 4.0 approach to revolutionize the transfer from laboratory to production using data-rich and cognitive computing technologies.
- Developing automated self-optimizing reactors for multistage processes, with Dr Reddy's. We are looking to expand the applicability of self-optimizing systems and explore multi-step optimizations.

You can read more about these projects on our lab website (www.bournelab.co.uk)

I'd like to highlight my current Senior Research Fellowship with the Royal Academy of Engineering, in collaboration with AstraZeneca, which is enabling us to explore methods to quickly generate optimized libraries of compounds for clinical trials.

FURTHER READING

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Navigating Technology Transfer for LNP Formulations

Technology transfer can be a challenge with any drug product, but even greater vigilance is needed with more complex formulations, like lipid nanoparticle-based drugs

By Larry Beiter

A clear advantage of lipid nanoparticles (LNPs) and traditional liposomal formulations is their structural similarity to naturally occurring biological vehicles; as a result, they are generally well tolerated by the body. Increasingly, LNPs are being used to deliver highly specialized therapeutic molecules, such as oligonucleotides, which are seeing increased attention in drug development because of their ability to tackle disease on the genetic level (1).

The focus on oligonucleotides has translated into more research on LNPs, including the best ways to approach manufacturing and analytical challenges. Despite the growing body of research and scientific knowledge, LNPs remain a complex area that necessitates expertise beyond the formulation work required for more traditional therapies. The stability profile of the finished formulation is very dependent on lipid selection and the manufacturing process. The development of an LNP-formulated drug product can be a daunting task unless one has preliminary data to work with or previous experience with lipids. Because of this, it is common for drug developers to seek out an external partner with the right expertise to assist with the challenges.

Technology transfers are common in the pharmaceutical industry – a result of the prevalence of outsourcing and collaboration. But the process can be difficult for LNPs or liposomal products, which are inherently complex and require a more comprehensive manufacturing and testing approach. Naturally, more precautions must be taken; for example, in-process stability is a concern, and an expanded test panel is required to evaluate all critical quality attributes. Compared with a typical parenteral formulation, there will be more unit operations and analytical methods being transferred for an LNP formulation, and the manufacturing environment may need a higher classification.

Perhaps the biggest challenge is the journey into the unknown. Many LNP formulations involve novel payloads or APIs, and interactions between the various raw materials are not always fully understood. The supply chain requires careful and collaborative scheduling, and as such, a successful tech transfer will often rely on parallel transfer and development efforts at raw material suppliers.

Common questions, unique answers

When looking for the partner who will ultimately be working on your drug product, you need to ask questions. At Exelead, the most common question asked by potential clients is about our experience. Clients, understandably, want to know their project is in experienced hands – and that's at least one easy question for us to answer, as we've worked with many LNP products. Exelead currently supports 15 ongoing liposomal and LNP projects across preclinical, clinical and commercial landscapes and has been supporting the GMP manufacturing and testing of liposomal and lipid-based drug products for over 20 years.

Clients also like to ask how long a project will take. The answer to this question depends on many variables. We can move through a project very quickly, but it depends on how far the client has progressed with formulation and process development. If a client has a functional formulation with an idea of the key methods for GMP, we can be manufacturing clinical batches within a year. If a client only has knowledge of the API and a research paper or two, then additional time needs to be invested in laboratory development to establish a robust formulation. We have the expertise to help companies at any stage, but generally the speed of a project will relate to current development progress and pre-planning. As early as possible, the team must agree on the scope of work and the project boundaries in terms of raw material supply, final product presentation, batch size, product specifications, and client or supplier responsibilities. In our experience, selection of standardized materials and components always helps to facilitate and accelerate the transfer. For instance, if the client can accept a vial and stopper combination that we have already validated, it will save both time and money associated with component procurement and validation. The transfer and scale up to GMP manufacturing will also be smoother if we can use our existing qualified suppliers and existing qualified raw materials.

Another question that often comes up relates to engineering batches, sometimes referred to as test batches or pilot batches. Are they needed – and, if so, how many? The API and raw materials are often very expensive for LNP formulations; manufacturing operations may extend across multiple days, and more than one batch may be required to confirm critical parameters and replicate the quality attributes defined at the laboratory scale. Companies can be reluctant to spend money manufacturing batches that won't be used in the clinic, but successful clinical batches are dependent on the ability to work out the bugs in the process, verify batch records and supporting documentation, and confirm process parameters. The engineering

batches ensure we can transition to repeatable GMP manufacturing and provide a reliable clinical supply. Engineering batches can provide additional value by generating the requisite process material for validation activities, such as sterility-related method validation and filter validation. These materials may also be suitable to supply GLP animal studies. We understand that the need to verify design of the process prior to GMP production must be balanced with the finite supply of raw materials and resource.

At Exelead, as soon as we begin evaluating a request for proposal, we start initial process design activities, including identification of unit operations and equipment requirements. We devote process engineering resources, validation and laboratory resources to your project before we've even signed a contract. We start by creating standardized block flow diagrams that identify key equipment, unit operations, testing requirements, and key parameters that need to be maintained. We want to have as much understanding of your manufacturing process as possible, and ensure the scope of work and the proposal address all the necessary decisions and assumptions required to clear the way for the tech transfer team to be successful.

We follow our block flow diagrams with a project definition document that identifies all of the project assumptions. This document includes assumptions related to process design, validation, method transfers, raw material supplies, packaging requirements, outside studies, and more. We put these detailed assumptions down on paper and incorporate them into the proposal to clearly define project scope and provide full clarity for the project team. In some cases, aspects such as method transfers may already be finalized at the proposal stage. That allows us to get started quickly once a contract is signed. Depending on how far the process has been developed by the client, initial steps usually include some evaluation of process operations and methods in a laboratory setting. While those evaluations are happening, we finalize the block flow diagrams and process descriptions, and establish a validation plan.

A team effort

Getting the final drug product to the clinic – and eventually over the finishing line of final approval – is very much a team effort. You need to be confident in your chosen partner. My golden rule for choosing the right company to work with: take time to adequately gauge their level of interest and engagement. Your partner should be as dedicated as you are when it comes to getting your product to market. You should expect them to ask difficult questions about process and product robustness, manufacturing scale, method reliability, and your experience. If they provide limited technical details in their proposal, tell you everything will be fine once the project starts, or show little interest in discussing potential problems? Definitely a red flag.

Communication is key. You need to be prepared for active discussions throughout the project. Any risks or issues should be raised as quickly as possible – ideally during the initial proposal stage. This allows for a comprehensive project plan that avoids problems before they can negatively impact schedule or cost. However, if issues do arise during the tech transfer, the important thing is to quickly address and rectify them. The focus should be on getting back on track as quickly as possible.

My advice to drug manufacturers is to ask questions as early as you can. Don't wait until the contract is signed. Working together to develop a solid base design early will lay the foundation for success – and from there you can focus on continued evaluation and optimization.

Larry Beiter is Director of Process Engineering & Development at Exelead

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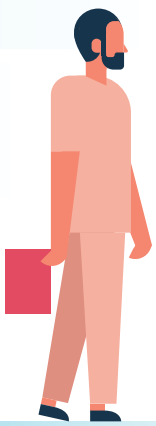
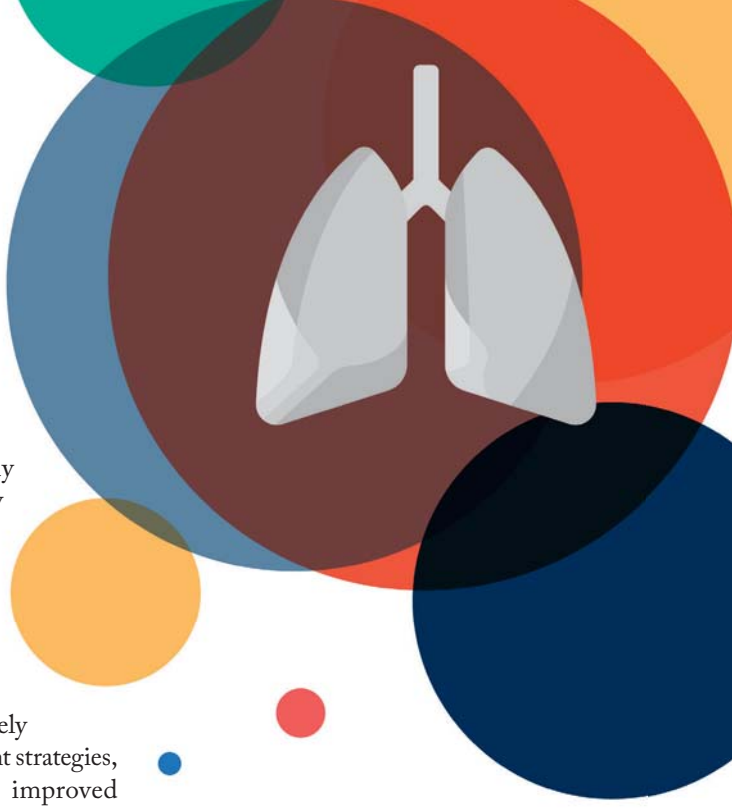
Best Practice

Technology
Quality
Compliance





Breathing New Life into Existing Drugs

Inhaled administration has the potential to bring benefits to patients – and commercial success to businesses – across a number of therapeutic spaces. But how do you identify the best opportunities for drug repurposing or repositioning?

By Geraldine Venthoye

Finding new uses for old drugs is now a significant trend in the pharma industry. There can be some inconsistency about terminology, but generally speaking, a repurposing project will take a drug already approved for one indication and seek approval for another or, alternatively, a new formulation may be created to allow administration via a different route for the same indication. A repositioning project, meanwhile, tends to take an existing drug and give it an improved or altered product profile, while keeping the same administration route. Either way, as well as providing advantages for patients, repurposing or repositioning can also be used to extend intellectual property (IP) coverage and drive additional revenue for innovators. Drug repositioning now accounts for almost a third of all new drug products, generating half a trillion dollars in annual sales across all dosage forms (1).

Inhaled administration offers significant repurposing opportunities; only a relatively small number of medicines made their first appearance on the market in inhaled form. A number of drugs that are today very familiar in inhalers started life in another delivery format, including beta-2 agonists, anticholinergics, and corticosteroids, as well as antibiotics, such as tobramycin and aztreonam. Though most are locally effective products – notably those designed to treat respiratory disease – some are systemically targeted, such as drugs to treat diabetes, migraine, or Parkinson's disease.

Repositioning is more likely to reflect lifecycle management strategies, whether by providing an improved inhaled delivery mechanism, or offering patients improved dosing regimens. It is also possible to use the inhaled route to dose more than one drug at the same time, opening up opportunities for new combination products. Alongside the actual drug and its formulation, an improved delivery device can also encourage enhanced patient adherence.

Faster and cheaper

Repurposing or repositioning a drug is often a faster and more affordable way to develop new products than de novo drug discovery and development. Attrition rates are lower, as the active will already have passed safety trials, and less preclinical testing is required, with inhaled toxicology the main tests potentially needed. The reduced timescales needed for the project also translate to lower costs.

Inhaled products can offer therapeutic advantages over oral or injected dosage forms, even if they are not used to treat diseases of the lung. One of the most important benefits that the inhaled route offers is fast onset of action. If the molecule is inhaled sufficiently deeply into the lungs, the speed with which it is taken up by the bloodstream is almost as fast as administration by injection. This rapid uptake has been exploited with orally inhaled insulin products, such as Affrezza (MannKind) and Pfizer's now-withdrawn Exubera, as well as with products aimed at treating pulmonary arterial hypertension, such as Bayer's Breelib (iloprost). Other conditions where speed could be a distinct advantage include pain relief, particularly migraine, and in Schizophrenia, bi-polar disorders, and Parkinson's disease, where rapid onset would be desirable to treat acute symptoms. Inhaling a drug also avoids first-pass metabolism of the liver that occurs with oral dosing, which can enhance the activity of a drug that may be broken down quickly through hepatic metabolism or by the digestive system. Avoiding this metabolism may also make beneficial changes to the metabolite profile, which is particularly important if a drug has known metabolite-related adverse events.

On the life-cycle management front, a drug approved for an adult might undergo repositioning for the pediatric market, and this may or may not include changing the delivery mechanism; for example, from a pressurized metered dose inhaler (pMDI) to a smart nebulizer or a dry powder inhaler (DPI) to suit the expanded patient population. Children may find it particularly difficult to

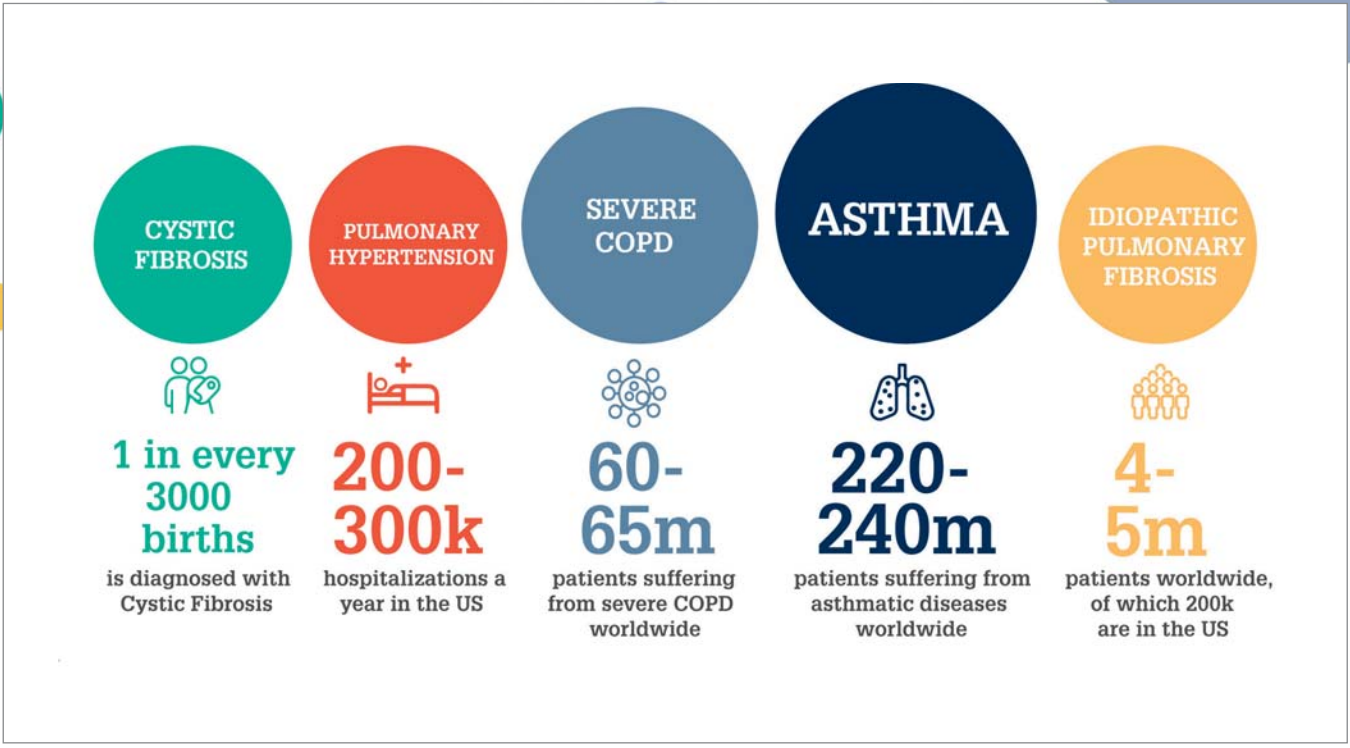


Figure 1. Patient prevalence in the respiratory market. Sources: WHO, British Lung Foundation, GSK, BI.

synchronize inhalation with a pMDI and may have less user errors with a DPI or nebulizer presentation.

Of course, there also has to be a therapeutic rationale for the change. The starting point should, therefore, be to determine an unmet therapeutic need, and how market share and commercial value might be derived from meeting it. For innovators, improving patient compliance is important because if patients take a drug correctly and therapeutic benefits are established, it will likely result in more prescriptions being filled. In inhalation, there is ample opportunity to improve upon the delivery method. For example, metered dose inhalers can be difficult for patients to use correctly because of the requirement to time the dose with breathing in, so advanced devices that improve patient use and compliance are important. An innovative delivery device can also provide an additional layer of market protection from competition.

Identifying the right niche

Looking more closely at clinical need, the global respiratory market obviously continues to be the most attractive. Significant unmet patient needs remain in asthma and chronic obstructive pulmonary disease (COPD), as well as more niche diseases, such as cystic fibrosis, pulmonary hypertension, and idiopathic pulmonary fibrosis, as shown in Figure 1, with some low volume but high value opportunities. Increasingly, the strongest growth potential lies in rarer diseases and systemic indications. The general market is growing at a rate of about six percent. But with cystic fibrosis, for example, the market is growing more quickly at >10 percent (see Figure 2 on page 32).). Drug designation for rare diseases can also come with other advantages, such as potential fast track designation, abbreviated approval processes, accelerated review, tax credits, fee waivers, and extended exclusivity – depending on the market region and regulator.

Systemic diseases, where delivery via the lung can benefit or enable targeting, offer substantial opportunities for drug repurposing. Drugs can be given a faster onset of action, while conserving potency, safety and tolerability. It can also be possible to dose within tight therapeutic windows, or to mimic the pharmacokinetic profiles that are achieved with the injectable drug delivery route. Inhaled administration can also be potentially used to effect mucosal vaccination.

A formalized and rational process should be used to identify the repurposing or repositioning projects most likely to succeed. The process should evaluate a product's potential against key criteria,

Examples of Differentiation and Improved Adherence

New technology – that benefits patients – is one way to differentiate a product from the competition. As an example, nebulizer devices have been designed to improve drug delivery using flow and volume control to better target the nebulized aerosol to the correct part of the lung, or within a specific type of inhalation profile. Modern devices are also breath actuated, which means they only nebulize while the patient is actively inhaling, and can also be Bluetooth-enabled so that treatment can be monitored via an app or a web portal to check adherence.

As a case in point, Vectura developed Breelib with Bayer, which was launched in 2017. This is a repositioned version of iloprost (Ventavis), which is used to treat pulmonary arterial hypertension. Without treatment, life expectancy is about three years, but with iloprost, this can often be extended to 10–12 years. However, the drug needed to be dosed nine times a day via a nebulizer, and each dose took 10 minutes to administer. Clearly, there was an opportunity for improvement.

Repositioning the drug into a Fox nebulizer allowed the dosing time to be reduced to three minutes through more efficient mesh nebulization with inhalation flow rate and volume control. Although this must still be done up to nine times a day, the total time spent dosing each day is reduced to under half an hour. The result is a substantial improvement in quality of life for the patient (2). The device also gives the patient feedback, leaving them feeling more in control of their treatment and their disease.

Another example is Mylan's TOBI (inhaled tobramycin) – a narrow therapeutic index aminoglycoside antibiotic used in the treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis (CF) patients. Tobramycin was originally administered by intravenous or intramuscular injection before being repurposed as an inhaled nebulized therapy. Local lung delivery by nebulization in CF is clinically proven to improve respiratory function, decrease hospitalizations and reduce the need for systemic antibiotic use. The latter is prone to induce adverse side effects. Some of these, such as nephrotoxicity and ototoxicity, are irreversible (3).

The TOBI Podhaler is a lifecycle extension of the marketed nebulizer product. This dry powder inhaler is a repositioned product, which reduces treatment burden whilst improving patient convenience. It achieves this by providing patients with a room temperature stable formulation, using a portable inhaler with no requirement for a power source or compressor. Administration time is also reduced from about 20 minutes to five minutes twice a day, whilst also eliminating the need to clean and disinfect the nebulizer. The beneficial impact on the CF patient's quality of life is significant in terms of their freedom from lengthy home administration of essential antibiotic therapy. And that may translate into better treatment cycle adherence and clinical outcomes (4).

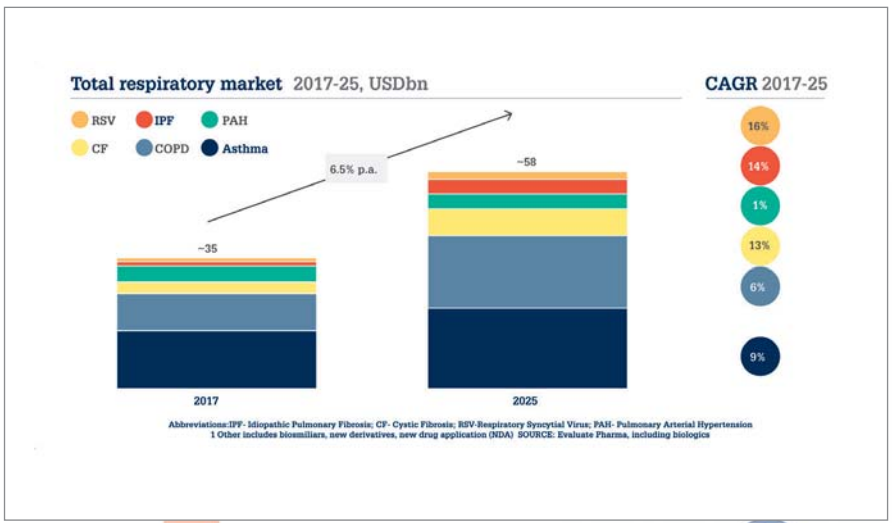


Figure 2. Total respiratory market. Data taken from EvaluatePharma.

to filter opportunities and short-list product concepts. The evaluation should consider business strategy, clinical needs, commercial opportunity, technical aspects, and overall feasibility (see Figure 3). As an example, there are an estimated 300 projects within development databases that could benefit from an inhaled dosing strategy. The first step should be a quick triage of potential projects' alignment to corporate vision and R&D investment strategy. This should still leave a considerable number of projects – perhaps around 100. The next stage of the filter is to consider clinical needs and market potential. An unmet medical need provides a

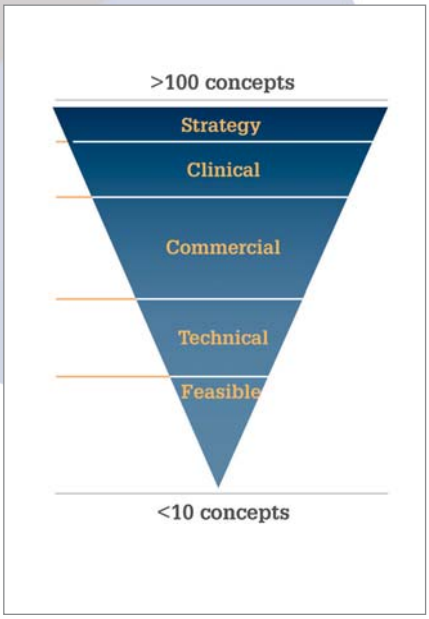


Figure 3. Key considerations in selecting an asset to develop.

compelling value proposition. Even if the condition is already covered by other products, the size of the patient population and the prevalence of the disease may still make the project viable. However, there should be a sound scientific rationale alongside the efficacy, safety and mechanism precedent.

The next consideration is commercial potential. It is important to judge how crowded the existing marketplace is, and whether a new product is sufficiently differentiated against the competition to offer both clinical and commercial value. Without these, it is unlikely that the drug will gain sufficient market share and meet reimbursement targets. Assessments also need to be made as to whether the desired value inflexion could be achieved within a reasonable timeframe, and whether the predicted return on investment is sufficiently attractive.

A commercially viable project will also need technical advantages. In-house proprietary technology, intellectual property, and improved functionality can all drive meaningful market differentiation. These aspects are also likely to provide product protection to deter direct competition.

The final filter is a project's feasibility. Successful inhaled delivery is notoriously complex to achieve, and there are barriers to entry from a practical perspective; can the drug be formulated and delivered as an inhalable aerosol, and can it be dosed consistently in sufficient amounts at the target site of deposition within the lung to be efficacious and safe? Research and detailed diligence should be undertaken to assess whether a project leverages a company's specific technical know-how, as well as the disease area and geographic focus. This final filter should leave just a handful of potential projects that meet all criteria.

De novo drug development is expensive and time consuming, so repurposing and repositioning existing drugs for new applications is extremely appealing from a commercial perspective. However, it's crucial that the evaluation process also considers the scientific rationale and how patients will benefit. There is particularly unmet medical need in lung diseases, both common and rare, and the opportunity to improve on drug delivery methods through more advanced devices for both asthma and COPD, but the opportunities don't stop with respiratory diseases – there is plenty of potential in the systemic delivery space too.

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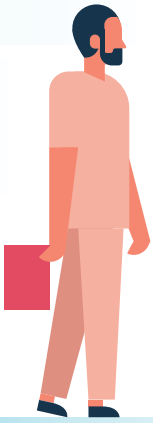
Mind the Skills Gap



SPECIAL SERIES
Advanced Medicine

The UK has an enviably strong advanced medicine R&D base, as evidenced by the high number of cell and gene therapy clinical trials under way – 12 percent of the world's total as of January 2020 (1). In January 2016, UK politicians and industry leaders set up an Advanced Therapy Manufacturing Taskforce to help support the sector. One of its main recommendations? We must address the skills gap. Here, experts from the UK discuss how the country is tackling this thorny issue.

By James Strachan and Maryam Mahdi

Finding New Talent

By Netty England and Kit Erlebach

Advanced therapy medicinal products (ATMPs) are opening up new therapeutic avenues for the pharmaceutical community, but despite the growing demand for cell and gene therapies, a significant skills bottleneck threatens to hold the industry back from its projected growth: the production process for ATMPs requires a highly-skilled workforce to maintain its operations – and there simply isn't a large talent pool to pull from.

The UK's Cell and Gene Therapy Catapult (CGT Catapult) published a report late last year detailing the skills demand of the industry – and there were clear concerns when it came to recruiting talent. Over 80 percent of respondents to an industry survey expressed their concerns about recruiting and retaining skilled individuals and highlighted a worrying fact: "a lack of skilled and experienced people will be one of the main issues that could slow down or cause a delay to the forecasted sector expansion" (2). Because of the complex nature of the CGT sector, individuals with prior industry experience in biopharma manufacturing are ideal to fill these roles, but the competition for these professionals is fierce. The question remains: how do we bolster the talent pool for CGT?

Any sector that wants to attract employees must be able to sell itself. For the CGT industry, this means building awareness of the real opportunities.

Attracting people to a career in CGT should be straightforward given the excitement of the field and the fact that it is developing truly ground-breaking medicines. Tapping into declining industries, such as traditional manufacturing, could also provide some of the staff required to maintain the growth of the CGT sector. These workers are well-accustomed to operating in regulated environments and could become a competent source of individuals, with the right training courses. However, this would only address part of the problem. New talent is also needed to fill the skills gap, but another concern highlighted in the report is the fact that many academic courses are not producing graduates and postgraduates who are industry-ready, limiting the number of professionals able to enter the industry with the competencies required to fulfill the roles that are and will become available (2).

Apprenticeships will be crucial to bringing in new talent and will help people understand the opportunities that lie in the pharma industry. When thinking of careers in medicine and health, many people do not think about the pharma industry at all! In the UK, the government aims to create quality occupational pathways through the development of employer-led apprenticeships (3). The Advanced Therapies Apprenticeship Community, or ATAC, is one example of an initiative developed to attract new talent to the field. Launched by CGT Catapult, the program helps professionals and fresh talent develop the skills and competency needed to manufacture ATMPs at scale. The CGT Catapult was awarded £1.5 million by the UK government to set up the initiative in response to the Advanced Therapies Manufacturing Action Plan, a report published by MMIP highlighting the measures needed to ensure the future success of the ATMP industry (4). The action plan outlined six measures that the industry would need to take for the "long-term management" of the sector. These measures included:

- Strengthening and securing an internationally competitive fiscal landscape to attract investment
- Targeting and capturing internationally mobile investment
- Maintaining science and innovation funding
- Setting out an end-to-end talent management plan to secure relevant skills for emerging manufacturing technologies
- Identifying predictable and viable routes to market
- Developing long-term regulatory strategies

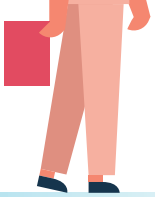
With the aim of contributing to a robust talent management plan and addressing the outlined measures, ATAC has launched apprenticeships to develop talent in STEM careers beyond healthcare. Its recent UK roadshow is one example; ATAC's experts met with employers, teachers and career advisors to educate them about the options available to students in the CGT space and promote the rewards of a career in advanced medicine as well as the advantages that taking on apprentices bring to employers (5). ATAC currently delivers a range of different apprenticeship programs that develop the technical skills, scientific knowledge, and professional behaviors of 72 apprentices across 27 companies and this is growing.

To further encourage companies to take on apprentices, the UK government introduced its Apprenticeship Levy. The levy, which was first introduced in 2016, applies to businesses whose total yearly salary expenditure amounts to £3 million or more and is used to take on and train apprentices (6). The initiative has now been extended to ensure that small and medium enterprises,

The Industry Has Spoken

A report published by the UK's Cell and Gene Therapy Catapult surveyed over 95 percent of UK ATMP developers to identify their concerns. Its findings showed:

- Of the companies who participated in the survey, only one did not expect to increase its talent pool over the next five years.
- Insufficient access to talented staff will limit the UK ATMP sector's growth.
- Though survey respondents believe that the Advanced Therapies Apprenticeship Community is positive, it will only account for up to 10 percent of the skill demands. The vast majority of the future workforce will be transferred from other regulated industries (up to 60 percent) and through the recruitment of graduates and postgraduates (up to 30 percent).
- Employees competent in data management and the use of automated technologies will be another essential part of the ATMP workforce, with 63 percent of respondents citing the importance of digital skills for the industry.



who can't pay the levy based on their earnings, can still access apprenticeships.

Beyond apprenticeships, academic institutions are also taking steps to "industrialize" their students. Universities now offer integrated and specialized modules, as well as postgraduate courses, that prepare students for the realities of the ATMP working environment and equip them with practical skills. In 2019, for example, iMATCH (one of the Advanced Therapy Treatment Centres (ATTCs) across the UK) partnered with the University of Manchester to develop a masters course to ensure students had the choice to select modules covering various ATMP indications (7). Many universities across Europe have also taken similar steps. Organizations like the League of European Research Universities (LERO), however, believe that more can be done to secure the ATMP workforce. In a report published in 2019, the European organization argued that more funding would be required to ensure the "continuity of staff employment as well as career development" and to work toward the "predicted pipeline" of the therapeutics the industry aims to develop (8).

Retaining experienced professionals

As well as bringing in new talent to the CGT sector, we also need to ask how we retain seasoned professionals and develop the next generation of leaders.

In the UK, the BIA Manufacturing Advisory Committee, which was set up to support the country's commercial biomedicine manufacturing community, launched its pilot leadership program (LeaP) in 2017 to upskill the workforce. LeaP brings together professionals from the biomedicine and CGT communities, with the intention of building interdisciplinary networks and giving employees from across the UK's scientific sector the skills necessary for taking on more senior company roles. Participating companies give their employees the chance to visit other companies' worksites, share best practices, and identify ways of improving their own operations. The program also encourages ATMP companies to learn from companies whose experience lies outside of life sciences and pharma. Last year, a participating cohort of companies visited BMW to learn about the flexibility of their assembly lines and evaluate what could be applied to their own practices.

In the years since LeaP was first set up, the program has trained and provided mentorship to two cohorts of life science and CGT companies and continues to support these companies to further build industry ties through its alumni network.

When considering the workforce of the future, we also need to think about how technologies are changing. Digital tools, in particular, are on the rise. This was highlighted in a report published by the Science Industry Partnership. The UK-based organization's Skills Strategy 2030 collated research that identified skills gaps across the country's scientific sector. It also highlighted that a failure to integrate IT, artificial intelligence, and machine learning into business practices would be a significant challenge for the ATMP sector (9). The report noted that professionals with specialist knowledge of computer-aided design and manufacturing would be essential for the future of ATMP manufacturing as the industry shifts away from manual processing. On an international scale, pharmaceutical companies are, however, moving toward increased collaboration with technology companies, and working to improve their employees' digital literacy. This was highlighted at the 2020 bioProcessUK conference, where speakers from Microsoft and GE (now Cytiva) addressed the ways the industry could better apply learnings from the tech sector to benefit future generations of drugs. And the relationship between the two industries is not one-sided. Going forward, companies from both industries must be able to identify the things that drive progress within the other and train their staff to adopt these practices for their mutual benefit.

Creating a robust workforce will be a challenge for the ATMP sector, but it couldn't come at a more exciting time for the industry. The ATMP sector is rapidly growing around the world. And as patients begin to benefit from advanced therapies, the number of people interested in playing a role in their development will likely also increase.

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Much in Demand

In conversation with Stephen Ward, Chief Manufacturing Officer at the UK's Cell and Gene Therapy Catapult

Why are new people crucial to the success of the cell and gene therapy industry?

There's a skills gap across the global cell and gene therapy industry today – everyone needs more skilled people. It isn't stopping companies starting or growing now, but it will restrict the growth potential of the industry over the next couple of years, unless something is done to remedy the situation. In the UK alone, the industry will need 3000–4000 new skilled recruits over the next four or five years to enable it to grow at the rate we think it can.

Which roles are most in demand? And how can the industry address the skills gap?

There are a number of hotspots in manufacturing, with quality assurance skills certainly in demand today. We know that companies want the majority of new staff to have industry experience, but we also know there aren't enough of these people in the cell and gene therapy industry to go around. So how do we square this circle?

Although there might not be enough workers with the exact skills required, there are people in other industries with an abundance of transferable skills. Companies might not think of poaching someone from the food sector, but food is a highly regulated industry, and someone who understands quality assurance for one sector should be able to apply it to another – with some training. The same goes for engineers (who are also in short supply). There are facility engineers in the automotive, robotics and semiconductor industries that are running highly complex processes, following detailed instructions in a routine way. They might not have biology PhDs, but these are the right transferable skills for cell and gene therapy manufacturing. As an industry, it's about boxing clever. We can't conjure highly trained staff with direct industry experience out of thin air. Taking workers with the right transferable skills from other industries – especially declining ones, as Netty England and Kit Erlebach said – will be the key to success.

How is the Cell and Gene Therapy Catapult addressing the skills gap?

In addition to attracting staff from other industries, the cell and gene therapy sector must also be willing to retrain the staff it already has, as the industry grows and develops new requirements. The Cell and Gene Therapy Catapult collaborates with universities to run training courses that allow professionals within the cell and gene industry (and students) to learn in-demand skills. For example, our aseptic manufacturing course, which we launched in collaboration with the University of Hertfordshire, teaches a mixture of theoretical knowledge and practical application. Students learn the principles and operational aspects necessary for aseptic manufacturing of cell and gene therapy products (in line with European regulatory guidance), as well as what is practically involved in running a state-of-the-art cleanroom facility (1).

The University of Hertfordshire is close to the cell and gene therapy cluster we've built in Stevenage (where the CGT Catapult manufacturing center is located). And similar courses could be rolled out in collaboration with universities adjacent to the other cell and gene therapy clusters across the UK.

Does it make sense to look at the skills gap for the advanced medicine industry as a whole, or do the cell and gene parts have different needs?

"However, I believe, paradoxically, that the biologics and small molecule sectors will end up learning from autologous cell therapies."

There are plenty of similarities: both cell and gene therapies are new, advanced medicines – and so they are part of the same "story." And many cell therapies have a gene modification step, which involves similar skills and has similar bottlenecks. There are also a lot of similarities in terms of how to control and automate data. But there are some important differences too. For example, autologous therapies are patient specific and require parallel, multi-batch capabilities, with very intensive supply chain management considerations for consumables and for the transport of patient material. It's almost like an Amazon Prime operation where everything is meticulously tracked to ensure nothing goes wrong. Gene therapies are more analogous to traditional batch processes. The gene therapy industry is perhaps where the biologics industry was several decades ago – the major challenges being how to purify, harvest and characterize a product. It, therefore, has a great deal to learn from the biologics sector and its employees.

However, I believe, paradoxically, that the biologics and small molecule sectors will end up learning from autologous cell therapies – and the skills of its members. The sector is rapidly learning how to deliver personalized medicine at an increasingly large scale, where the patient is the focal point of the supply chain. I can see the next generation of small and large molecules also being far more personalized than we've seen in the past. Those sectors will be looking to autologous cell therapy engineers and scientists for tips, as they'll be the ones with the skills to make personalized medicine a reality.

Why has the UK emerged as a leader in the CGT space?

The UK is one of the premium centers for cell and gene therapy primarily because of the skills base we have in the R&D community. But we've also managed to create a connected ecosystem, from research through to manufacturing and delivery. I think one of the advantages we have in the UK is that we're quite a densely populated country, which enables connectivity within the sector and allows for things to happen quite quickly – with the Catapult network acting as a lever. In addition to filling the skills gap, the UK needs more investment into new companies with proper capitalization. And that's where the US really comes into its own. That said, I think the UK does fare well on the investment front when compared with the rest of Europe. The real challenge for the UK cell and gene therapy sector will be making sure our SMEs reach a commercial inflection point and then, when they do, giving them good reasons to keep operations in the UK.

Ireland's cell and gene therapy industry serves as an interesting comparison. Ireland's National Institute for Bioprocessing Research and Training (NIBRT) has been successful in delivering a skills agenda for Ireland's booming biopharma manufacturing economy – and I can see Ireland replicating this success for the next wave of advanced medicines. But one major challenge for Ireland is that, despite their strength on the manufacturing side, they don't have the same R&D capabilities as the UK. Companies in the cell and gene therapy space that have invested in an R&D team want close links with their manufacturing teams. The two cannot be separated easily in this space and there's a lot they can learn from each other. The UK may have an advantage there. But it isn't a zero sum game. I think there's great potential to learn from each other and to collaborate to help the advanced medicine industry thrive on both isles!

What would you say to someone considering a career in the advanced medicine sector?

I would simply ask whether they want to be involved, on a daily basis, in translating science into cures – because that is the potential of this medicine. We're not only managing disease, but providing life-changing and even life-saving therapeutic benefit to patients. It's also a fascinating field to be involved in. The basic science is one thing but we're also seeing rapid innovation in manufacturing, with digitalization and artificial intelligence ready to change how we deliver these therapies. We're going to need disruptive thinkers and a new generation of people coming through for the cell and gene therapy industry to reach its full potential.

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Profession

Your career
Your business
Your life

Devoted to Men's Health: Lessons Learned with Robert Dudley

Robert Dudley, Chairman, CEO and President of Clarus Therapeutics, guided the development of the blockbuster testosterone replacement therapy, AndroGel. Here, Bob reveals his lessons learned and shares how he has tackled the challenges around a newly launched TRT – the first oral softgel approved by the FDA.

Success happens at the convergence of passion, tenacity, collaboration, and significant unmet needs

How I got to where I am today feels somewhat serendipitous. With a PhD in pharmacology and toxicology, my background is in drug development and examining how drugs work. Early on in my career, I joined a small entrepreneurial company called Gynex Pharmaceuticals that had an interest in testosterone replacement. It was my first foray into the world of testosterone replacement therapy, which we fondly abbreviated to TRT.

My initial work was on a sublingual testosterone product licensed from the NIH in the US, but its pharmacokinetic profile necessitated thrice daily dosing and the FDA was concerned about peak well above the upper limit of normal for testosterone. After a stint as VP of Clinical Development at a biotechnology company (BioTechnology General Corp.), I took a job as Vice President of R&D at Unimed Pharmaceuticals. It was here that I was approached by Besins Iscovesco (Paris, France) about developing a dihydrotestosterone (DHT) gel product as an androgen replacement therapy for men. Besins already had a DHT gel approved for use in France and Belgium but felt it could do well in the US. My response was, "Well, no – the FDA will not embrace a DHT gel because of concerns (at that time) about DHT's potential role in prostate cancer." Nevertheless, I went on to tell the company that I would be interested in collaborating with their team on a testosterone gel (T-gel) formulation...

Out of these initial discussions, AndroGel 1% was born and eventually approved by the FDA in 2000. I am really proud of this success. For such a small company to help develop the formulation, conduct all the clinical studies, and do everything else required to launch a product really is an amazing achievement. It was also a lot of fun! I guess history is the best gauge of AndroGel's success; until AndroGel 1.62 percent gel came along, it

was the top-selling testosterone product in the world.

This was when I learned how important collaboration is. In our case, we were working with partners across an ocean, which demanded some flexibility. We also connected with some of the top academic investigators in TRT, and their expertise served as our base of operation from a clinical point of view. On a personal level, I made some incredibly dear friends – and mentors – who stuck by me through the whole process. As a result, I'm a strong proponent of using cross-functional teams aligned to do something pretty spectacular – whatever that may be.

Unimed also gave me the opportunity to move into the role of President and CEO (and at a public company) when my then predecessor left the company. From this position, I built the team to commercialize AndroGel and later, along with David Dodd (then president of Solvay Pharmaceuticals), I was the co-architect of the sale of Unimed to Solvay. After the sale, I remained President of Unimed until my decision to move back to the pharma startup world.

The good, the bad, and the ugly; honesty really is the best policy

As my career in pharma evolved, I became more aware of the fact that men with low testosterone have a seriously diminished quality of life – and it's not just about reduced libido! These men have multiple issues that often sum up to a poorer quality of life. Moreover, the available therapies didn't seem entirely optimized to patients' needs – they simply weren't designed to encourage patients to stay on their medication. After developing AndroGel, I left my role as president and CEO of Unimed Pharmaceuticals and started to consider what was still missing from the TRT marketplace. The answer: a safe and effective oral testosterone formulation that meets current regulatory standards for efficacy and safety. After all, oral medicines are more convenient for the patient than an injection or topical gel.

"As my career in pharma evolved, I became more aware of the fact that men with low testosterone have a seriously diminished quality of life."

With that goal in mind, my current chief financial officer, Steve Bourne, and I began (literally) knocking on the doors of venture capital firms and pitching the idea. That's how we started Clarus Therapeutics where we developed Jatenzo (testosterone undecanoate) capsules, CIII – an oral softgel TRT that was recently launched in the US after FDA approval in March 2019.

But developing Jatenzo turned out to be a formidable task! After launching Clarus, we spent the first 18 months investigating something that didn't work. I went back to our investors to admit our lack of success and to propose an alternative. The lesson here: be brutally honest. You need to be honest (with yourself and others) about where you are, so you don't chase something that's bound to fail. Our investors said they'd continue to back us, and we switched gears and worked to develop the successful formulation that would become Jatenzo. I believe that honesty was crucial in keeping our investors on board.

Drug development setbacks succumb to good problem solving

Setbacks come in all shapes, sizes and varieties; you need to get used to them in the business of drug development. For technical challenges, you must be a good problem solver. You have to get not only your own mind wrapped around the challenge, but also the minds and hands of other people who can help. Focus on the data; (generally) data don't lie. And be flexible – expect to make some changes to formulation parameters to advance the product.

You also need to get your development plan right and get into humans as fast as possible. There are all sorts of great animal models out there, but the animal that matters most when it comes to accurate results is the human.

Those three things – good problem solving, accurate testing, and speedy human trials – plus persistence, of course – are the lessons I've learned to achieve success. I've often used the analogy that drug development is like sailing into the wind. You just have to find a way to make forward progress until the winds come back around to fill your sails. Have faith that you can do it, and don't give up as long as the business thesis remains sound. In the case of Clarus, despite our sometimes-daunting challenges, no other company came forth with an oral testosterone product and beat us to FDA approval. So, the market opportunity also remained strong.

"Setbacks come in all shapes, sizes and varieties; you need to get used to them in the business of drug development."

Don't fear the regulator – you're both on the same team

It has been a long, winding path to get Jatenzo approved by the FDA – a combination of internal development challenges and more rigorous evaluation requirements by the FDA that evolved during Jatenzo's development. When it comes to the FDA, I have never lost sight of the fact that they have a tough job. I respect what they have to do very much, and I know they want the same thing we do: to make sure patients get the effective, safe treatments they need. Although I might not have agreed with all the hoops the FDA required Clarus to jump through for Jatenzo, I always viewed our relationship with the FDA as one of collaboration. We knew that we had to do our utmost to be responsive to their questions and requests and to maintain a good dialogue on what would be necessary to secure Jatenzo's approval.

Our path to approval for Jatenzo was made more difficult by the success of the AndroGel franchise that ultimately ended up in Abbott's (then AbbVie's) portfolio. Here was a product that was heavily promoted in a direct-to-consumer campaign that the FDA and many physicians did not like – largely because there was concern that T-products were being over-prescribed. Beyond that, in 2014 and 2013, there were some controversial papers that indicated a possible cardiovascular risk associated with TRT. And so, the FDA started to look more closely at the TRT development arena, and, over time, they tightened regulatory requirements.

When I developed AndroGel, it was a much less rigorous regulatory path than by the time I got to Jatenzo. As a result, I think we likely provided more data and information on our oral testosterone product than any TRT product before it. And we went before two separate FDA advisory committees during which the FDA explained that Jatenzo would likely change the landscape of TRT therapy and, thus, the need to make certain it was thoroughly reviewed.

Launching a new drug demands full-spectrum planning and top-notch execution

Upon approval of Jatenzo, our top priority was an excellent and well-executed launch. We launched the product in the US only a few months ago and we have worked hard to ensure that healthcare providers (HCPs) and patients are aware of Jatenzo and have access to it through their insurance plans. Access to prescription medicines is a big challenge worldwide, but, in the US, the insurance companies that oversee pharmacy benefits have become more selective about which drugs they cover, and how these drugs are included in the respective formulary plans.

We will continue to strive to maximize patients' ability to easily access the medication in ways that are not a major hassle for their HCPs. The first year is all about establishing and growing momentum after the launch to build receptivity in the marketplace. Then, we'll begin to look at additional projects that feed into lifecycle management. We believe there is still room to improve the treatment experience for patients – and we think that'll keep us very busy for the next couple of years!

Men's health is rife with needs – and therefore, opportunities

Short-acting injections and patches were not the kinds of TRT products that men wanted, according to our market research. Jatenzo is a prime example of identifying an unmet need and addressing it. Looking at other diseases and health issues that affect men, I can see a lot of room for improvement. Inevitably, even incremental progress can make a big difference to patients. Consider testicular cancer – thanks to research and treatments, the cure rate is near 100 percent when it's caught sufficiently early. Other cancers, such as prostate cancer, particularly refractory cancer that has metastasized, have not seen the same progress, but this may change given that many companies are looking at new treatment approaches.

Male contraception is another area where progress has been slow. That said, there are some really interesting studies coming out of the NIH and elsewhere that indicate that a male birth control pill could be closer than we initially thought. There is a significant group of the male population that would benefit from this form of contraception.

Beyond those, there is a cultural issue that affects men's health. Many men simply avoid regular visits to the doctor, reluctant to admit they have a problem. Getting men to take better care of themselves is another unaddressed issue. This is especially significant in the big categories of cardiovascular disease, diabetes, and neurological issues, such as Parkinson's and Alzheimer's. Anything we can do to make it easier and more comfortable for men to talk about their health and get the help they need could go a long way toward reducing that reluctance.

At any given time, you may have no idea just how important your work is – keep at it

I was somewhat surprised by the success of AndroGel, even though I thought it was a major advancement in TRT when it entered the market. What I underappreciated at the time, and what epidemiology studies have since supported, is that testosterone deficiency is much more prevalent than had been assumed. In that context, it was all the more important to develop a product that would be used by appropriate hypogonadal men. Most types of hypogonadism that have structural or genetic causes require men to be on testosterone for the rest of their lives, so finding a convenient dosage form that encourages long-term compliance is crucial. And I hope Jatenzo will continue this story. Though our efforts with Jatenzo have been primarily focused in the US, we'll be filing applications in the EU and in Asia over the next few years and also looking at other international opportunities. I think that's exciting, and I'm proud of what my then colleagues and I accomplished with AndroGel – and even more proud of what team Clarus has done to bring Jatenzo to the market.

If you love your work, it will love you back

I love my work. I love the medicine. I love the science. I now have over 30 years of experience in this field, and it is hard to imagine stepping outside of it. I'm not saying that I wouldn't, or couldn't, change if the situation demanded it or the opportunity was interesting and challenging enough, but working in men's health issues is a calling for me. I've managed to find a career that continues to fascinate and energize me; it makes me feel like I'm making a positive difference for men. If you can manage to find a way to reap such rich internal rewards, you're blessed!

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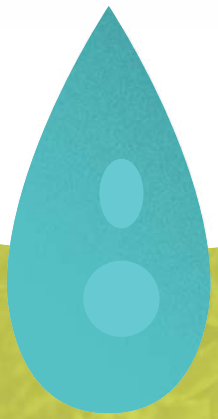

COVID-19: The Oral Vaccination Approach

An oral vaccine for COVID-19 is due to enter phase I clinical trials

Most vaccines are injected, but there is strong interest, for a number of reasons, in developing oral alternatives. Vaxart, a biotech company based in San Francisco, was founded with the aim of developing oral vaccines and has a pipeline of vaccine candidates for norovirus, influenza, HPV and more. Since January 2020, the company has also been exploring how its vector-adjuvant-antigen standardized technology (VAAST) could be used to create a COVID-19 vaccine. We spoke with Wouter Latour, Chief Executive Officer and Chairman of Vaxart, to learn more.

How did the company get started in the area of oral recombinant vaccines?

Our founder, Sean Tucker, is a mucosal immunologist who, in his early career, spent several years developing vector platforms to deliver genes to the gastrointestinal system for gene therapy purposes. He realized that vectors could also be used to deliver vaccine antigens to the gut, and so founded Vaxart with the aim of developing oral vaccines. The company's mantra is that a vaccine needs to be easy to make, easy to distribute, and easy to take.

What are the main challenges of developing these types of vaccines?

The first challenge was to develop a versatile vector construct that would selectively activate the immune system to generate a broad and durable immune response to the expressed vaccine antigen – and not to the vector itself. After evaluating multiple systems, we settled on non-replicating Adenovirus 5 (Ad5), in combination with a molecular adjuvant (dsRNA) optimized to activate the immune system of the gut. The second key challenge was to develop a tablet that could deliver the vaccine to the right location in the intestine. We've developed an enteric coated tablet that protects the vaccine from the acidic environment of the stomach and then releases the active ingredient in the small intestine.

The principle of oral vaccination is not new. There are some very successful oral vaccines, such as the polio and rotavirus vaccines, which are used widely around the world, but these rely on attenuated pathogens that replicate. The problem with this approach is that it can't be used to repeatedly deliver heterologous antigens because the immune system will generate anti-vector responses that neutralize the vector itself. To create an oral platform, we use a non-replicating vector (that doesn't elicit an immune response to the vector) and express a selected pathogen antigen along with the dsRNA adjuvant. The resulting platform produces an immune response preferentially to the antigen of choice. The platform can be used multiple times and with a wide variety of targets.

When did you start work on a COVID-19 vaccine program?

We started work on our COVID-19 vaccine program in late January 2020. As with other DNA and mRNA vaccine companies, our vaccine expresses key antigens of SARS CoV-2 in vivo. Once the sequences of SARS CoV-2 were published, the nucleic acids were synthesized and cloned into our Ad5 platform. Our Ad5 platform allows us to build multiple vaccine candidates very quickly, each based on a different coronavirus antigen combination. We were able to make vaccine candidates ready for preclinical testing in a matter of weeks.

We entered into an agreement with Emergent BioSolutions in March and, provided Vaxart elects to proceed, Emergent will be manufacturing the vaccine in bulk to allow us to initiate phase I trials.

What advantages do oral vaccines offer?

We think our tablet vaccines offer enormous logistical advantages in terms of manufacturing, distribution and administration. The manufacturing of our vaccine is performed with standard single-use bioreactor technologies, which are available at multiple major manufacturers. In addition, our vaccines are tableted using high-throughput industrial tableting machines that are, again, widely available in the pharmaceutical industry. They do not require sterile fill-and-finish in vials or needles – a major bottleneck in the production of injectable vaccines.

Finally, there is growing consensus that a large-scale vaccination program will

"There are some very successful oral vaccines, such as the polio and rotavirus vaccines, which are used widely around the world, but these rely on attenuated pathogens that replicate."

"There is growing consensus that a large-scale vaccination program will be needed to ensure the COVID-19 pandemic is contained and to protect against future infections."

be needed to ensure the COVID-19 pandemic is contained and to protect against future infections. We believe the advantages of an oral, room temperature-stable tablet vaccine for such an immunization program are very compelling.

What are the technical challenges of developing a vaccine for COVID-19 – compared with flu, for example? And what is the outlook for a COVID-19 vaccine – particularly if SARS-CoV-2 mutates?

One of the main challenges for flu is that multiple strains circulate at the same time, and the circulating viruses are constantly changing. And that's why there are quadrivalent flu vaccines, with the vaccine strains chosen each year based on what is predicted to be circulating. At this time, it is unclear if a single COVID-19 vaccine would be sufficient to protect against all circulating variants of the virus, or if the vaccines would need to be updated and, if so, how often. Our platform is versatile, so we could rapidly add new antigens if necessary. In my view, a key differentiator for our oral vaccine is that it does not elicit antivector immunity like the injected vector-based approaches – and this may be important if long-term immunity to SARS-CoV-2 requires more than a single immunization.

We have conducted multiple clinical trials with our flu and norovirus vaccine candidates based on the same Ad5–TLR3 platform and we have dosed more than 400 healthy volunteers to date. Our oral vaccines consistently generate both systemic and mucosal responses. Importantly, in a large phase II influenza challenge study, a single dose with our tablet vaccine offered the same protection as an injectable flu vaccine (1). What's more, our protection was primarily based on mucosal immunity, which may be critical for COVID-19. A mucosal immune response may also generate a higher degree of cross-reactivity than the systemic responses, as it has been shown that IgA is better at inducing cross-reactivity than IgG (2).

What steps will you be taking in the near future for this project?

Right now, we are moving our top vaccine candidates forward, and we will decide in the coming weeks which vaccine candidate we will manufacture for our phase I clinical study. That first clinical study will begin in the second half of 2020.

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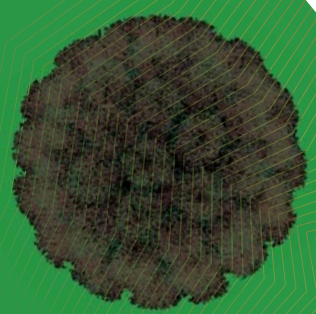

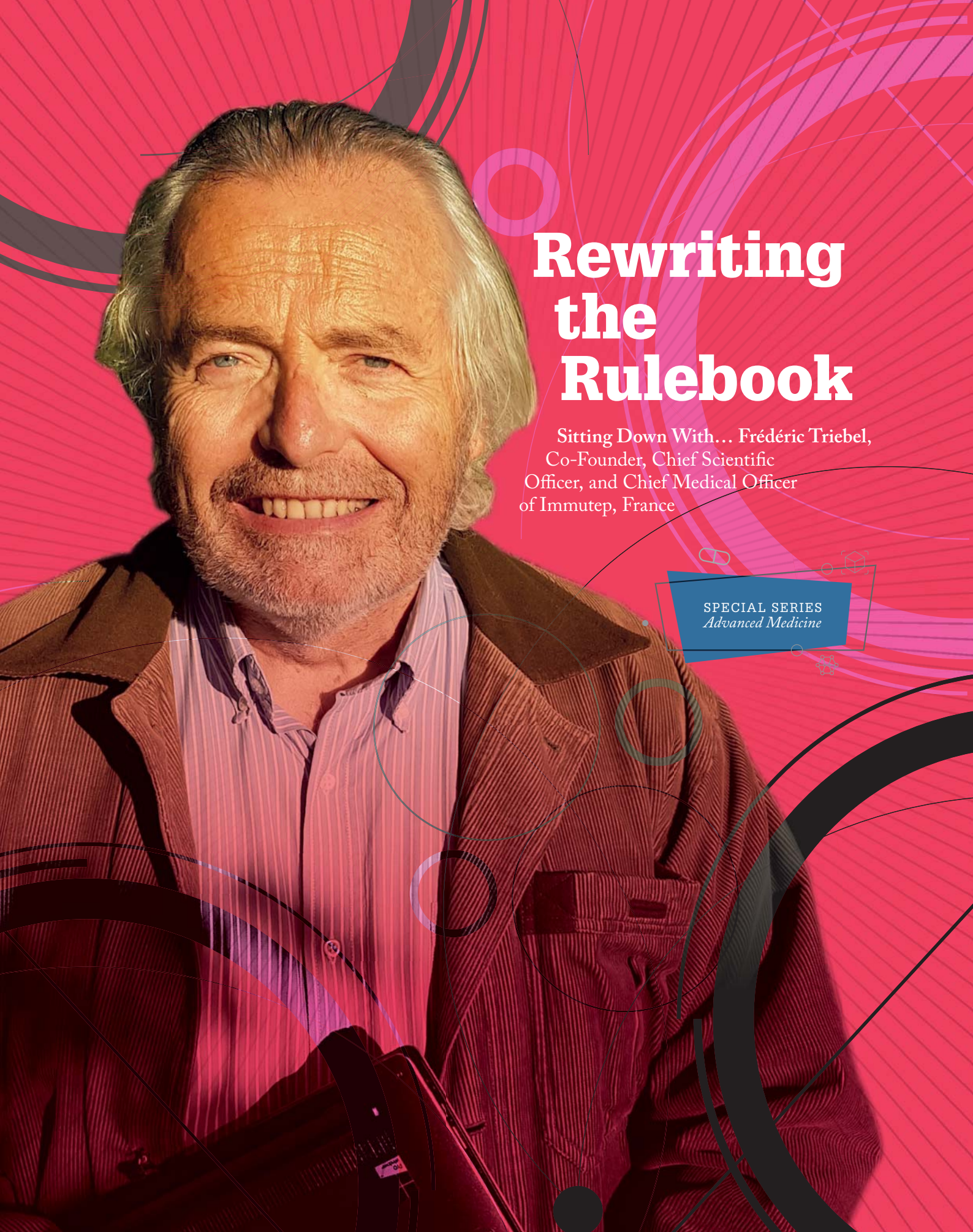

Rewriting the Rulebook

Sitting Down With… Frédéric Triebel, Co-Founder, Chief Scientific Officer, and Chief Medical Officer of Immutep, France

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Did you always want to be a molecular biologist?

I wanted to be a doctor when I was young, and I went to medical school when I was 16. I enjoyed the holistic view of science I received there – physics, chemistry, a bit of mathematics and statistics, as well as anatomy and physiology – and I certainly learned a lot. But working in a hospital essentially involves applying the rules you have learned. Though that is rewarding, I was more fascinated by the prospect of discovering new rules. We've known since the ancient Greeks that regardless of how much knowledge you have, there's always an ocean of the unknown. So I decided to put down the textbook and turn to the microscope.

What did you work on initially?

I started off in hematology in the 1970s, but switched to immunology – my thesis was on human T cell cloning. I then worked on sequencing human T cell receptors, which was new for the molecular biology field. At the same time, I was also working on tumor infiltrating lymphocytes – trying to see what kinds of T cells there were and why there are so many T cells in some human tumors. There were a lot of parallels with an autoimmune disease, which was a good sign if you're interested in cancer immunotherapy. We didn't know at that time why these T cells were not doing their jobs and killing the tumors. It's been fascinating to watch the gaps being filled in over the decades leading to the development of CAR T cell therapy and other immuno-oncology treatments we see today.

You are perhaps best known for discovering LAG-3. How did that come about?

I was at the University of Strasbourg for my second post doc using a new and sophisticated molecular biology technique that allowed us to clone new mRNA expressed specifically in activated T cells. And so, 30 years ago, I ended up discovering the lymphocyte activation genes, LAG-1, LAG-2 and LAG-3 – the latter proving to be an important checkpoint molecule for the immune response. But we also realized that there was a relationship with another molecule: CD4. We saw that they sat together on human chromosome 12 and thought that they might share the same ligand. A few years later, we were able to show that the LAG-3 protein was a ligand for MHC Class II molecules like the co-stimulatory CD4 molecule, and that LAG-3 function in the T cell was co-inhibitory. These molecules function like Yin and Yang – a balance between co-stimulatory and co-inhibitory activity, where a lack of harmony leads to problems like autoimmune diseases.

How has the checkpoint inhibitor field developed since your discovery of LAG-3?

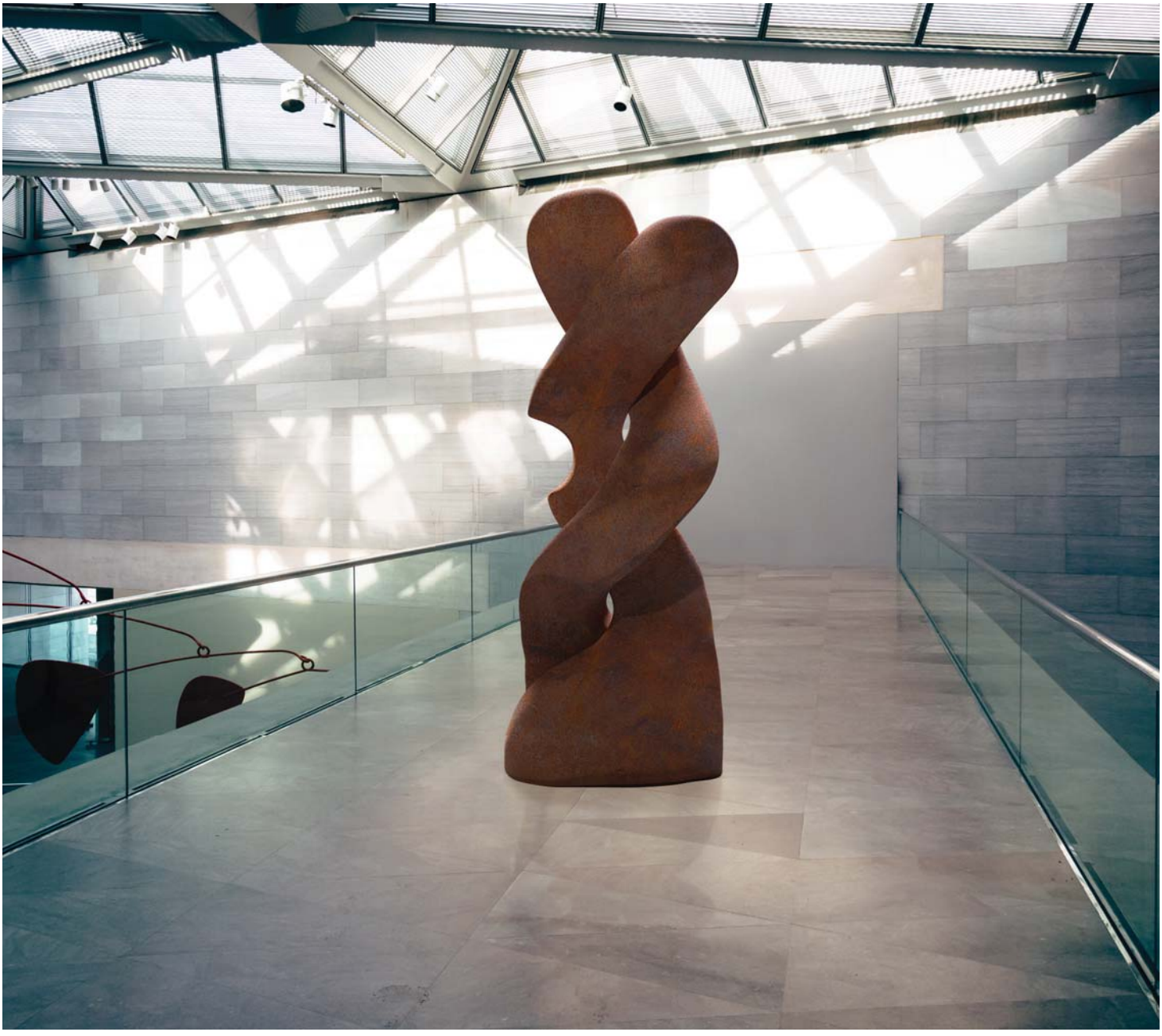
Just look at the numbers. Pembrolizumab (Keytruda) was registered by Merck in 2014 for melanoma – a small market – and it is a blockbuster, used in more than 22 indications. It's even replacing chemotherapy as a first-line treatment for lung cancer. But despite this success, if you look at metastatic carcinomas on the whole, the outlook for patients is bleak. These diseases are currently incurable and there have been few advances in treatment since the 1980s. I believe that we're on the cusp of something significant with more therapies aimed at treating a patient's immune system to enable the body to effectively fight cancer – in combination with other drugs. But the potential of the field extends to other indications too beyond cancer and auto-immune diseases. Consider how T cells attack endothelial cells and create the chronic inflammation we see in atheromatous patients, or the role brain inflammation plays in Alzheimer's disease.

How did you find the transition from research to industry?

Co-founding Immutep was not such a huge upheaval; I always wore many hats during my research career. For example, I was a professor of immunology teaching students, a clinician treating patients, and a biologist conducting research, but I was also helping to set up early stage clinical studies. I also worked with companies on cancer vaccines and observed how our industrial partners worked. I think this stood me in good stead to deal with a variety of different challenges in industry: be it manufacturing, budgets, regulation or investors. One thing I never tried to do is reinvent the wheel; I found a good, experienced partner – John Hawken – to help launch the company.

Have you faced any major hurdles during your career?

Many! You may go to a company's website and see that everything looks great, but behind the window dressing you'll always find challenges. A huge one is convincing investors to put their money behind an unproven and potentially risky approach. Again, basic research – where you're competing to be the first to publish – was good training. There, I learned resilience as many research projects fail. Just look at LAG-1 and LAG-2: we didn't end up with anything significant with those, but we decided to continue with LAG-3 because of the central importance of its ligand, MHC class II, in immunology. Finding LAG-3 was rather serendipitous, but I had to be confident that it would be worth working on for years – possibly decades. Convincing yourself, from the beginning, that something is worth years of your life is surely harder than convincing investors in the future!



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