NOVEMBER 2020 # 70

the Medicine Maker®

Making Medicine... Anywhere

How can biologics be made on-demand in deep space environments?

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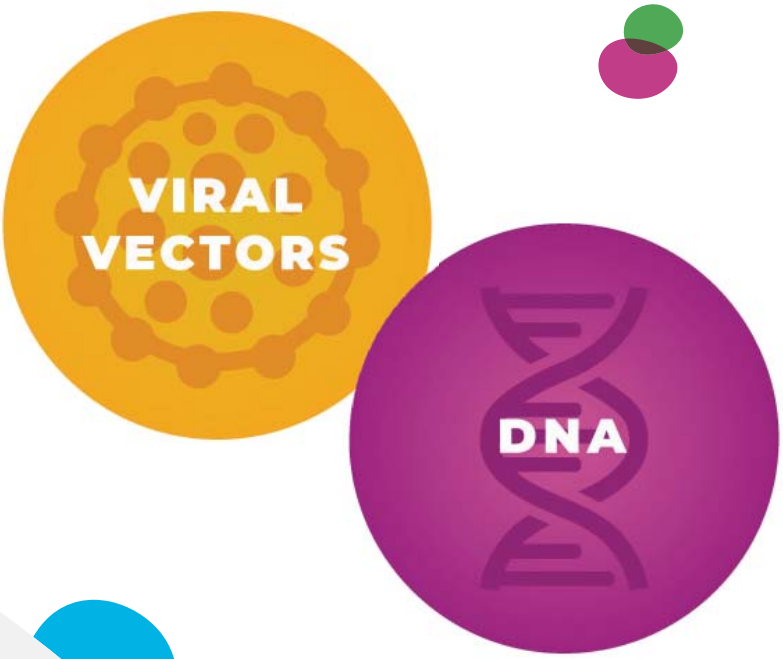

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Back in 2017, we explored what healthcare and pharma might look like in 100 years' time (1); the experts I spoke with were intrigued by the premise, but were quick to point out that it's hard to predict what will happen in five years' time – and so virtually impossible to imagine a world in 2100 (although they still tried!). As 2020 has proven, even six months can seem like a very long time. The term "COVID-19" didn't exist in November 2019, but by mid-March it was a household name, with most of us living in lockdown, trying to come to terms with how quickly a black swan event can transform our lives.

Right now, I don't know what 2021 will look like, but I do know that a single revolutionary medicine or vaccine could significantly transform the COVID-19 outlook. And the whole research and development community is working hard to bring us that breakthrough sooner rather than later.

But what lies beyond COVID-19? There are many diseases that could benefit from all the collaborative effort and funding being poured into COVID-19. What if the world could rally around malaria or tuberculosis in the same way? Vaccines and treatments already exist for TB, but it still killed 1.4 million people in 2019 (2). Experts have also expressed concerns about the pandemic's impact on the treatment of other infectious diseases (3); once the COVID-19 storm passes, it's likely we'll need a thorough reassessment of global healthcare priorities.

Where else can the wider pharma industry develop partnerships to bring about drastic improvements? Manufacturing seems like one area that could benefit; most vendors work alongside pharma partners, but few vendors work together – or with partners outside the industry – to develop truly revolutionary tools. And yet, working together seems like the fastest way toward disruptive change.

On that note, our cover feature looks at one provocative (and, if successful, disruptive) direction: the ability to synthesize biologic medicines in any location – even on Mars. Sound far-fetched? On page 18, scientists explain how it is possible, perhaps offering us a glimpse of what could lie on the post-pandemic horizon.

Stephanie Sutton
Editor

References

1. *The Medicine Maker, "November 2017 Issue of The Medicine Maker" (2017). Available at https://themedicinemaker.com/issues/1017*
2. *WHO, "Tuberculosis" (2020). Available at https://bit.ly/3mZQ6NE.*
3. *Nature, "How to stop COVID-19 fuelling a resurgence of AIDS, malaria and tuberculosis," (2020). Available at https://go.nature.com/3exUqAJ.*

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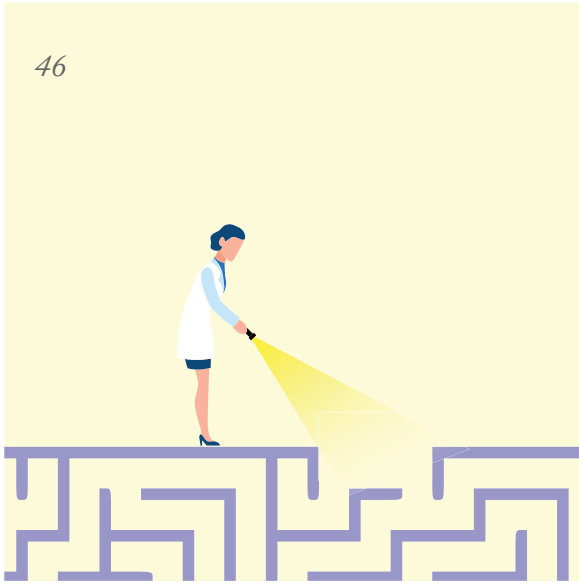

On The Cover

How are researchers tackling the issue of making medicines in deep space?

the Medicine Maker

ISSUE 70 - NOVEMBER 2020

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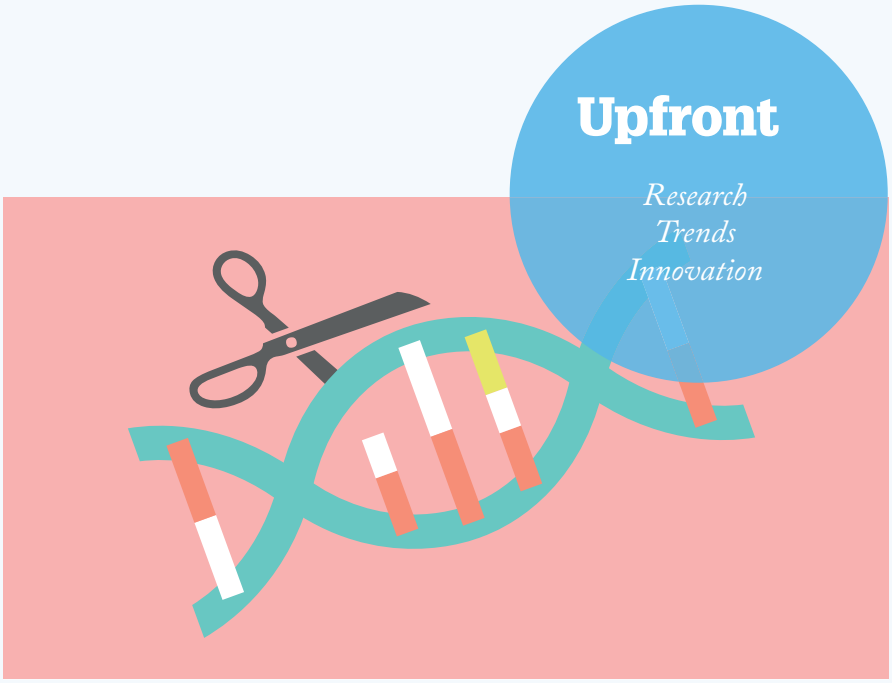


Informing Consent

Are seriously ill patients vulnerable to overestimating the benefits and underestimating the risks of gene editing studies?

As genomic editing trials become more common, it is crucial to ensure patients have full knowledge of the risks and benefits of experimental treatments. To discover what patients wanted (and needed) to know about genome editing to make informed decisions about trial participation, researchers at the US National Human Genome Research Institute spoke with patients, parents, and physicians in the sickle cell disease (SCD) community (1).

The team concluded that information about criteria for participation and quality-of-life post-procedure are important aspects of being informed. And though physicians expressed concerns about patient knowledge, adults with SCD and parents of children with SCD demonstrated greater understanding of the genetic concepts tested (genetic, chromosome, susceptibility, mutation, variation, heredity, and sporadic) than the general public – exceeding the expectations of physicians.

However, there were some misconceptions about genome editing procedures, as the transcripts showed. "I think it was when she talked about the embryo and changing the DNA of the embryo," one patient said. "In my mind, that's what I saw – a pregnant lady sitting on the table and they were digging in her belly button to get DNA from the embryo that's inside her and then changing it."

The Fort Lauderdale Physician Group was also concerned that current levels of uncertainty are not being expressed in conversations about CRISPR genome editing for SCD. "It may make things better. It is also possible that it will have a totally curative-type effect. I think we are not confident yet," they said. They also pointed out that patients need to know that a gene therapy may only be "curative" if done at birth. "If you wait until you have already suffered a stroke, renal disease, whatever other – and organ damage does occur, even if you have gene therapy, this is not going to reverse the damage that has already occurred. In that sense, it is not really a cure the way I think patients think it is a cure."

Reference

1. *S Desine et al., "The Meaning of Informed Consent: Genome Editing Clinical Trials for Sickle Cell Disease," AJOB Empir Bioeth, 11, 4 (2020).*

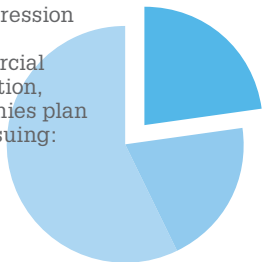
INFOGRAPHIC

Trends in ATMP Manufacturing

Cell and gene industry leaders look to automation as process development and optimization challenges loom

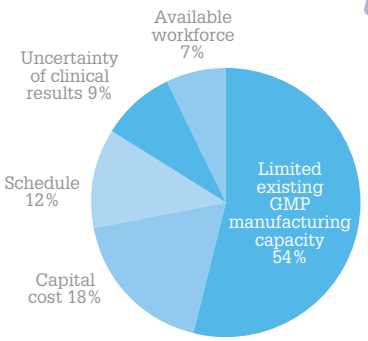
the Medicine Maker

In progression toward commercial production, companies plan on pursuing:



In-house manufacturing 23%
CMO/CDMOs 20%
Combination of both 57%

Top drivers influencing the decision to use CMOs/CDMOs:



ADVANCED MEDICINE IN BRIEF

A $4-billion acquisition, a key finding for sarcopenia drug development, and algorithmic efficiency… What's new in advanced medicine?

- Bayer is paying US$2 billion upfront and up to US$2 billion in success-based milestone payments to acquire gene therapy developer AskBio. AskBio has a pipeline of gene therapies, including programs for Parkinson's, congestive heart failure, and Pompe disease in early human trials. "Instead of going to Wall Street and every quarter trying to make milestones, we have one financial partner with which we're trying to bring this technology to fruition," said Sheila Mikhail, AskBio CEO.
- Losing muscle mass is a significant problem for older people and is partly due to a loss of the regenerative functions of satellite cells. Now, a team of researchers mainly based in Spain have found a subgroup of satellite cells that, due to FoxO activation, maintain their regenerative capacity over time, declining only at geriatric age. The scientists hope that their findings will help "harness the potential of stem cells for regenerative medicine in sarcopenia."
- Techniques to culture and control cells have improved a lot over the years, but finding the perfect conditions to keep undifferentiated cells alive and prevent them from acquiring a different cellular state remains tricky. Now, researchers in Singapore and Australia have developed a computational biology algorithm called EpiMogrify, which predicts factors that maintain cell state in vitro and identifies factors that induce cell conversion. The team reported a significant increase in the efficiency of astrocyte and cardiomyocyte differentiation using EpiMogrify-predicted factors for conversion conditions.

Want to stay up to date with all the advanced medicine news each week? Subscribe – for free – to The Cell + Gene Curator: www.texerenewsletters.com/covid19newsletter

Allogeneic Advance

A step closer to an off-the-shelf CAR T cell therapy

Two-out-of-four patients in a 300 million-cell cohort, and one-out-of-three in a 100-cell cohort, achieved a complete response following treatment with CRISPR Therapeutics' allogeneic CAR T cell therapy CTX110 (1).

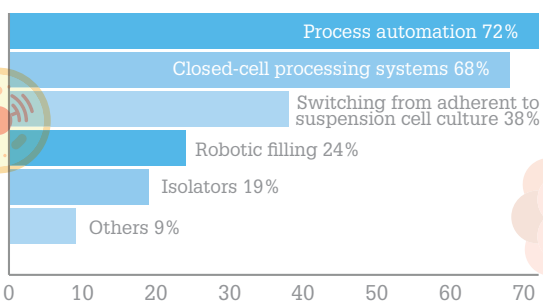
The B-cell malignancy treatment was safe at the 300-million dose level and below. The only patient who received a 600 million-cell dose, after initially achieving a complete response, was hospitalized with febrile neutropenia and later died after reactivation of HHV-6 and HHV-6 encephalitis.

CTX110 is derived from healthy donor T cells, which are modified using CRISPR/Cas 9 to i) insert a CAR construct, which binds to cancer cells and activates T cells and ii) knock out the T cell receptor and MHC1, which reduces the risk of graft versus host disease and rejection.

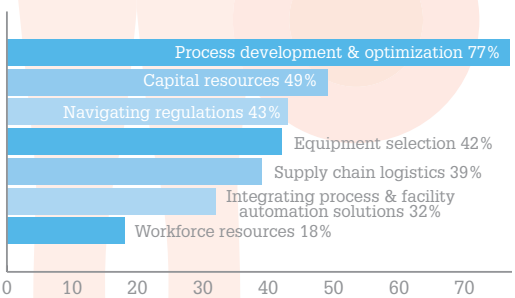
Reference

1. *CRISPR Therapeutics (2020). Available at: https://bit.ly/2TxT5Ag*

Near-term technology advancements expected to have the most impact on the manufacturing process:



Biggest challenges in progressing toward commercial manufacturing:



Source
CRB, "Cell and Gene Therapy" (2020). Available at: https://bit.ly/3IYzD4q

Poisoning Pain

Investigating the pain-relieving properties of spider venom

Offering an alternative to conventional analgesics, newly published research suggests that two compounds derived from the venom of the Venezuelan Pinkfoot Goliath tarantula could be useful in managing pain associated with irritable bowel syndrome (IBS) (1).

IBS affects up to 11 percent of the world's population (1). Symptoms include constipation and/or diarrhea, and abdominal pain, which can be severe. NSAIDs and opioids have been tested as pain management solutions, but have proved ineffective for most patients.

"Historically, treatments for IBS have focused on trying to normalize the effects of the condition on gastrointestinal motility, but this has had little effect on visceral (internal organ) pain" says Stuart Brierley, a professor at Flinders University, Australia, and the project's co-lead, adding: "Furthermore, opioids cause constipation, which poses significant problems for patients who already suffer from it. These types of drugs also fail to target both the gastrointestinal tract and the nerves that send pain signals from the gut to the brain."

The team chose to investigate tarantula venoms based on earlier studies that indicated their potential for blocking specific ion channels involved in visceral pain. "We screened a broad range of spider venoms using high-throughput sodium channel assays," says Richard Lewis, a professor from The University of Queensland's Institute for Molecular Bioscience and co-lead on the project. "Our study identified two novel peptides in the venom of the Venezuelan Pinkfoot Goliath tarantula that block Nav1.7 – a sodium channel ion expressed in pain-sensing neurons."

The researchers also found that the spider venom-derived compounds were capable of inhibiting calcium channel pain targets, including Cav3.2. According to Lewis, this combination "was particularly useful in reversing IBS pain." Next, the team hopes to optimize the structure of the compounds to improve their activity at pain targets and reduce side effects.

Reference

1. *FC Cardoso et al., Pain [Online ahead of print] (2020). DOI:10.1097/j.*

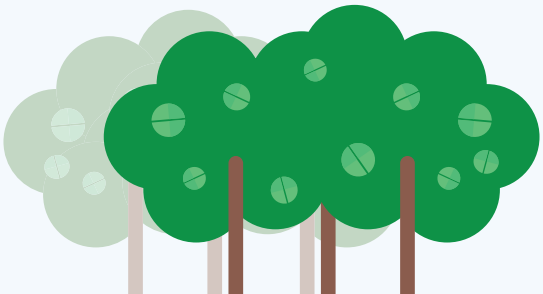
Green Trials

Small changes in clinical trials could benefit the environment

How can companies lower the carbon footprints of clinical trials? Kayentis – which provides electronic clinical outcome assessment (eCOA) solutions – has given the matter some thought. According to their estimates, 70 percent of the company's carbon footprint is linked to their eCOA projects – and over three-quarters of this comes from the production of smartphones and tablets required for clinical sites. It's clear that reducing the number of devices manufactured could make a big difference.

The company suggests that an online platform could be used to directly enter patient data, rather than stockpiling spare devices on each site. It also recommends that companies consider refurbished devices. The lifespan of a device is around four years, so refurbishing is a feasible solution for both short-term studies and replacing a device during the course of a study.

"Faced with the threat of climate change, every company and each individual has a key role to play in reducing the global carbon footprint," Kayentis CEO, Guillaume Juge, said in a statement.



Breaking New Ground

Construction begins for the Medicines Manufacturing Innovation Centre in Renfrewshire, Scotland, UK. The center stems from a collaboration between the UK's CPI, the University of Strathclyde and founding industry partners, AstraZeneca and GSK.

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QUOTE of the month

"International mail and express consignment are major conduits for drug smugglers. This has become more challenging for law enforcement as volumes have skyrocketed, and because of e-commerce and rapid shipping logistics."

US Customs and Border Protection Acting Commissioner Mark A. Morgan on the agency's collaboration with the FDA to prevent illegal drug imports. https://bit.ly/3kKSyHc

Mass Spec Meets Machine Learning

Can machine learning offer mass spectrometry a boost for drug discovery?

Researchers from Purdue University believe that combining machine learning and tandem mass spectrometry could improve drug discovery. Interpreting mass spectra for drug discovery can be challenging and time-consuming, so the team developed a decision tree model trained on 36 known ion-molecule reactions with 2-methoxypropene (MOP), a neutral reagent used to differentiate between isomeric drug metabolites. In the paper, the researchers explain that the model "uses the graph-based connectivity of analytes' functional groups as input to predict whether the protonated analyte will undergo a diagnostic reaction with MOP (1)." The model can characterize complex mixtures and identify chemical reactions and drug metabolites by predicting how compounds will interact with MOP in a tandem mass spectrometer.

One flaw of machine learning methodologies is that they can be difficult for humans to interpret, so the Purdue team has developed chemical reactivity flowcharts that can help users understand the mass spectra for structural information.

Reference

1. *J Fine et al., Chemical Science (2020).*

The COVID-19 Curator

Your roundup of the key scientific studies and industry announcements emerging from the pandemic

Our weekly newsletter collates the most impactful scientific news to come out of COVID-19 and delivers it straight to your inbox. Subscribe: https://www.texerenewsletters.com/covid19newsletter

Here, we roundup a selection of some of the latest and greatest research studies and company announcements about COVID-19 from October 2020.

Industry news

The FDA has approved remdesivir (Veklury) for hospitalized COVID-19 patients (adults and pediatric patients over the age of 12 – and weighing at least 40 kg). The approval is based on three clinical trials – one of which was conducted by the National Institute of Allergy and Infectious Diseases. According to the WHO's Solidarity trial, however, remdesivir does not reduce mortality or reduce recovery time for COVID-19. The same trial also found that hydroxychloroquine, lopinavir-ritonavir, and interferon beta 1a all had little or no effect in COVID-19 patients. The trial involved more than 11,000 adults in 30 countries.

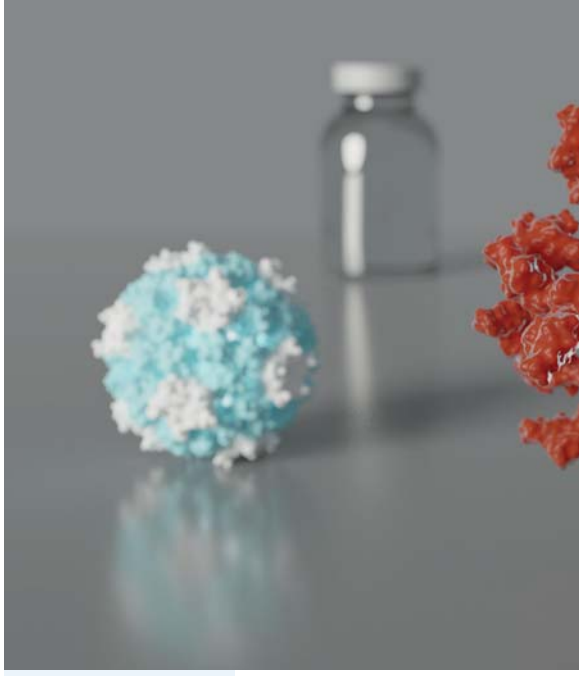
The EMA is implementing extra transparency measures for COVID-19 medicines by publishing clinical data that supports the authorization of remdesivir and information on COVID-19 treatments and vaccines that have received scientific advice or informal guidance from the agency's Pandemic Task Force (COVID-ETF). The EMA already had a policy in place to publish clinical data supporting marketing authorization; however, this was suspended at the end of 2018 due to the agency's relocation from London to Amsterdam. It remains suspended due to various pressures and human resource constraints, but the agency says it will strive to publish data for COVID-19 medicines. The clinical data is available at https://clinicaldata.ema.europa.eu.

Regeneron has been told to modify its trial for REGN-COV2 (a "cocktail" of two monoclonal antibodies) by the independent data monitoring committee. Specifically, the company has been advised to put a hold on enrolling patients requiring high-flow oxygen or mechanical ventilation because of a safety signal and "unfavorable risk/benefit profile." Enrollment of other patients will continue.

CureVac has reported interim data from its ongoing phase I dose-escalation study of CVnCoV, an mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of SARS-CoV-2. The vaccine has been well-tolerated across all tested doses (2-12µg) and induces strong binding and neutralizing antibody responses, as well as indication of T cell activation. Phase IIb/III studies are expected to begin by the end of 2020.

Early research

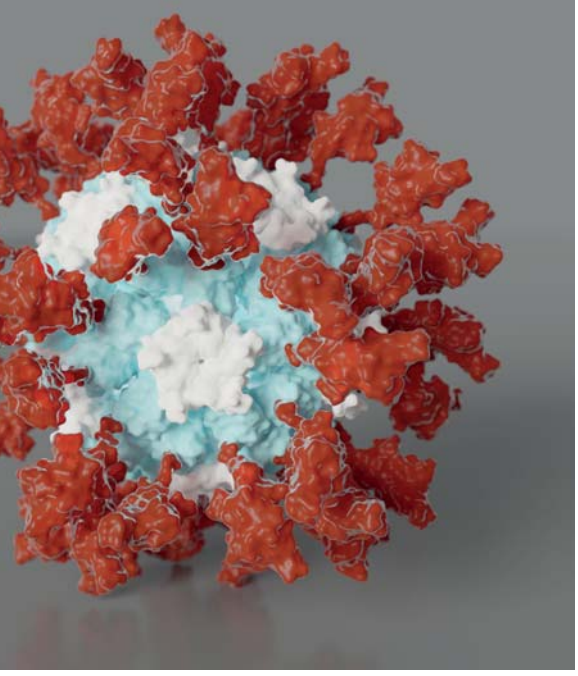
Jelly investigations. Autopsies of deceased COVID-19 patients show a clear liquid jelly in the lung alveoli. Researchers say this jelly consists of hyaluronan, a polysaccharide that binds to water. Existing drugs, including cortisone, can reduce production of hyaluronan and may reduce the amount of jelly in the lungs.
U Hellman et al., "Presence of hyaluronan in lung alveoli in severe Covid-19 – an opening for new treatment options?" Journal of Biological Chemistry, (2020).



Nanoparticle vaccine. Scientists at the University of Washington School of Medicine in Seattle have designed an "ultrapotent" nanoparticle vaccine against COVID-19. The vaccine's molecular structure roughly mimics that of a virus – and the team claim it can produce ten times more neutralizing antibodies in mice than the leading COVID-19 vaccine candidates – at a much lower vaccine dose. The vaccine is described as a "self-assembling protein nanoparticle that displays 60 copies of the SARS-CoV-2 Spike protein's receptor-binding domain in a highly immunogenic array".
AC Wells at al., "Elicitation of potent neutralizing antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2," CELL (2020). DOI: 10.1016/j.cell.2020.10.043.

Other avenues

Defining efficacy. A review article explores challenges in assessing efficacy of SARS-CoV-2 vaccine candidates and suggests routinely applying standardized, quantifiable endpoints across trials.
SH Hodgson et al., "What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2,"



The Lancet (2020). DOI: 10.1016/S1473-3099(20)30773-8

Knowledge gap. Analysis of COVID-19 publications has shown that basic microbiological research on SARS-CoV-2 is lacking. Though perhaps understandable during a pandemic, this relative lack of lab-based studies is unique when compared with research into other coronaviruses.
A Doanvo et al., "Machine Learning Maps Research Needs in COVID19 Literature," Patterns, 1 (2020).

Triple weakness. By studying host-virus protein interactions in SARS-CoV, SARS-CoV-2, and MERS-CoV, an international consortium of almost 200 researchers has identified key molecular mechanisms for all three viruses as well as potential drugs that could be repurposed.
DE Gordon at al., "Comparative host-coronavirus protein interaction networks reveal pan-viral disease mechanisms," Science (2020). DOI: 10.1126/science.abe9403

T cell therapy. T cells from recovered COVID-19 patients and multiplied in the lab have been found to maintain the ability to target proteins essential to SARS-CoV-2 function.
MD Keller et al., "SARS-CoV-2 specific T-cells Are Rapidly Expanded for Therapeutic Use and Target Conserved Regions of Membrane Protein," Blood (2020). DOI: 2020008488

Convalescent crisis. The PLACID trial in India, involving 464 patients, shows that convalescent plasma is ineffective in preventing progression to severe COVID-19 or all-cause mortality.
A Agarwal et al., "Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)," BMJ, 371 (2020). DOI: 10.1136/bmj.m3939

Cautious hope. Tocilizumab may reduce mortality of critically ill COVID-19 patients by counteracting inflammatory cytokine release syndrome; researchers urge caution over findings.
S Gupta et al., "Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19," JAMA Internal Medicine [Online ahead of print] (2020).

Feel the G. Vaccines modeled on the D-strain of SARS-CoV-2 are still effective against the now globally dominant G-strain and so vaccine-matching each season should not be required, according to the authors of a study.
AJ McAuley, "Experimental and in silico evidence suggests vaccines are unlikely to be affected by D614G mutation in SARS-CoV-2 spike protein," NPJ Vaccines (2020).

Understanding COVID-19

Immunity indecision. Studies seem divided on the longevity of antibody-based immunity to COVID-19, with some new studies revealing that robust neutralizing antibodies persist for months even as others show significant drops in population antibody positivity.
P Figueredo-Campos et al., European Journal of Immunology (2020). DOI: 10.1002/eji.202048970; A Wajnberg et al., Science (2020). DOI: 10.1126/science.abd7728; H Ward et al., "Declining prevalence of antibody positivity to SARS-CoV-2: a community study of 365,000 adults" [Online ahead of print] (2020).

Different strokes. A publicly available genetic analysis tool has detected and categorized regional SARS-CoV-2 variations, showing transmission routes and revealing mutation-resistant areas of the genome.
Z Zhao et al., "Genetic grouping of SARS-CoV-2 coronavirus sequences using informative subtype markers for pandemic spread visualization," PLOS Computational Biology (2020). DOI: 10.1371/journal.pcbi.1008269

No signs. A recent study of 36,061 UK residents showed that 76.5 percent of those testing positive for COVID-19 were asymptomatic; 86 percent lacked COVID-19-specific symptoms.
I Petersen, A Phillips, "Three Quarters of People with SARS-CoV-2 Infection are Asymptomatic: Analysis of English Household Survey Data," Clinical Epidemiology (2020). DOI: 10.2147/CLEP.S276825

Small, but mighty. "Mini-lungs" that mimic alveoli damage caused by SARS-CoV-2 show how, 60 hours after infection, alveolar cells start to disintegrate and damage lung tissue.
H Katsura et al., "Human Lung Stem Cell-Based Alveolospheres Provide Insights into SARS-CoV-2-Mediated Interferon Responses and Pneumocyte Dysfunction," Cell Stem Cell, [Online ahead of print] (2020). DOI: 10.1016/j.stem.2020.10.005

Sweet (pre)disposition. Diabetic patients may be more vulnerable to SARS-CoV-2 through primed kidney cells. Moreover, higher ACE2 receptor levels found in both diabetes and kidney disease may trigger severe COVID-19.
R Menon et al., "SARS-CoV-2 receptor networks in diabetic and COVID-19–associated kidney disease," (2020). DOI: 10.1016/j.kint.2020.09.015

In My View

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

Brexit Trading Unknowns

Is your business prepared for Brexit? Here's my advice.

By Nik Kotecha, Chief Executive of Morningside Pharmaceuticals Ltd, Department for International Trade (DIT) Export Champion and a CBI Regional Councillor, UK

As the famous quote goes, there are known knowns, known unknowns, and also unknown unknowns. And that very much applies to the current Brexit negotiations between the UK and the EU. We know there are red lines on both sides, but the overall outcomes are still unknown. What is clear to me and my company is that businesses must prepare for every eventuality – and start right now (if they have not done so already). Post-Brexit EU trade deal negotiations are continuing, but the UK will come to the end of the Transition Period on December 31, 2020.

But the first question for UK businesses: Where should we start? The best source of information, if you are just beginning the process, is gov.uk/transition where you can find the latest government guidance on preparing for the end of the transition period. For most pharma businesses, the guidance on importing and exporting goods with the EU is particularly important. If you can't find the answers you need, you can also make use of an enquiry service run by the Department for International Trade.

My company manufactures and supplies generic medicines to both the UK and international markets. We are actively making plans to mitigate any disruption to our import and export activities from the EU, particularly with our supply chain. There is no import duty on "finished" pharmaceutical packs, but we are concerned about disruption to our supply chains and the time taken to get products to destinations through customs. We're also checking tariffs that may be payable under the new UK Global Tariff that will apply to goods imported from around the world, unless there's a trade agreement in place.

One of the most important actions we've taken is to apply to be an Authorized Economic Operator (AEO), which is an international standard accreditation given by HMRC, which shows that our supply chain is safe and secure. It also ensures that the holder may be able to benefit from arrangements under Mutual Recognition Agreements, which are agreed with third country customs authorities. To achieve this, a business must submit an application to UK Revenue & Customs, which is then followed by an audit and inspection of the security and supply chain. To help prepare for the audit, we conducted a gap analysis to further improve our processes, which were fully reviewed in line with the criteria. We believe that the AEO (c) and (s) standards will keep us in good stead when it comes to trading not only with the EU, but also with the rest of the world.

For importing, businesses will have to make customs declarations when importing goods from the EU. Be aware that from January 1, 2021, the rules for importing some types of goods will change. You should also make sure you have secured an EORI number starting with "GB," checked the rate of tax and duty, and looked at ways to speed up the importing process.

All export shipments to the EU will also require a customs declaration, and you will need to be aware of licensing requirements and rules for the goods you export. For example, the rule for pharmaceuticals entering the EU is that any product being

"But the first question for UK businesses: where should we start?"

used in the EU, and going to an end patient there, must be batch released by a Qualified Person within the EU.

Pharmaceuticals manufacturers and suppliers are proactively taking action to ensure there is no disruption to the supply of medicines. You may wish to look at what action your logistics partners are taking. For example, some haulage providers are taking part in Alternative Routing, which is worth exploring and may help avoid delays at Dover, UK, and Calais, France.

In the event of a no-deal Brexit, we have built contingency plans to release batches for our patients in the EU through a site in the Republic of Ireland. Having an EU base will also enable us to comply with EU regulations around pharmacovigilance and the licensing of medicines in the EU from an EU territory. Another high priority for us is to work with the UK Department for Health & Social Care to ensure we are able to continue to supply our patients in the UK, as well as exporting medicines to patients who need them "on time" – especially as the risks of a second COVID-19 wave this winter are all too apparent.

My advice to businesses is to look at all of your known knowns and unknown knowns, and start preparing for the unknown unknowns – or, put another way, every eventuality. Only then will you be as prepared as you can be.

Precious Metal Catalysts: The Scavengers' Guide

Platinum group (and other precious) metal catalysts are routinely used to synthesize APIs – but they are inherently expensive, so why not recover and recycle?

By Philip Wheeler, Business Development Manager, Umicore Precious Metals Chemistry, California (USA). Dirk Rickert, Sales Manager, and Thorsten Rieke, Head of Marketing, Market Intelligence & Business Research, Umicore Precious Metals Refining, Hanau, Germany

There's no doubt that catalysis has played a significant role in the global chemical industry over the past few decades – recognized by numerous recent Nobel Prizes in Chemistry: Knowles, Noyori, and Sharpless' work for asymmetric catalysis (2001), Schrock, Grubbs, and Chauvin's work on alkene metathesis (2005), and Suzuki, Heck, and Negishi's work on the development of cross-coupling chemistry (2010).

In pharma, under constant pressure to reduce time to market for successful drugs, process chemistry teams must find the most cost-effective and scalable synthetic route as quickly as possible. At the same time, driven by the pursuit of increasingly difficult therapeutic targets, discovery teams are probing molecules that contain synthetically challenging motifs, such as macrocycles, spirocycles, and multiple stereocenters. To address the challenges presented by more complex structures, process development chemists have embraced new methodologies, many of which involve precious metal catalysis. For example, the development of macrocyclic protease inhibitors to treat hepatitis C infections led to the refinement and adoption of ruthenium-catalyzed ring-closing metathesis macrocyclization at the industrial scale (1).

Pharmaceutical manufacturers employ a variety of platinum group metal (PGM) catalysts to facilitate the production of APIs and regulatory starting materials. But doing so presents challenges, such as rising metal costs and the need to remove metal impurities. This latter challenge can be addressed by selecting the most efficient catalyst and limiting catalyst loading as much as possible. After loading has been optimized, attention turns to the removal of elemental impurities through various purification steps.

PGM catalysts are expensive – as you'd expect with precious metals – and subject to price fluctuations (PGMs are traded on the public market). And so, we believe it makes sense to consider a closed-loop approach to the catalyst lifecycle that makes the most of scavenging. The possibilities for scavenging are diverse – from simple charcoal slurry and filtration to more complex solutions, such as functionalized resins and silicas. The key is efficiency. Once a closed loop is implemented, the majority of the metal price is paid only once; recovered metal can be applied as credit toward future purchases of the finished catalyst. Moreover, as the recovered metal will be stored in metal weight rather than currency, it will be insulated from market fluctuations.

Implementing a recycling approach

"The possibilities for scavenging are diverse – from simple charcoal slurry and filtration to more complex solutions."

requires chemists to work closely with engineers, smelters, and supply chain experts to appropriately plan, design and implement the recovery solution. Collaboration and transparency between a refiner and manufacturer are vital to ensure the recycling plan is practical and effective. When choosing the right refining partner for a process, you should, of course, consider maximum recovery and fast processing turnarounds, but you should also think about transparency, communication, and overall support – just as you would with any outsourcing partner.

The refiner will need to obtain a representative sample of the overall spent catalyst and to understand how much of the PGM content in the catalyst is recoverable. Here, direct sampling techniques (without incineration) usually provide more accurate insights into a broad range of solid and liquid spent industrial catalysts. When sampling is completed, refiners must accurately and reliably measure the precious metal content of the materials being reclaimed, using a wide variety of sensitive analytical instruments and techniques.

Pharmaceutical companies are typically not able to sample and assay in-house, so you will be reliant on your refining partner. And that's why transparency – and trust – are so important.

The application of catalysis within the pharmaceutical industry is rapidly evolving. With the availability of novel laboratory tools for characterization, new approaches to synthesis and advanced computational capabilities, we have unparalleled potential for making significant advances in modern development. But as the industry continues to design innovative processes, let's not overlook the opportunities for precious metal recovery.

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Looking After Patients – Post-Pandemic

Manufacturers must consider adjusting their patient support programs to reach the increasing number of individuals struggling financially in the wake of COVID-19

By Corey Ford, Director, Reimbursement & Policy Insights, Xcenda

Among its many challenges, the COVID-19 pandemic has led to extraordinary economic upheaval. Specifically, the unemployment rate in the US has reached levels unseen since the Great Depression, with jobless claims exceeding one million for 20 straight weeks. GDP has seen the most significant drop on record. Initially, the pharmaceutical industry braced for a surge of patients in need of financial assistance following a loss of employer-sponsored health insurance. Though that expected surge in demand failed to materialize at the outset of the pandemic, it could be lurking on the horizon. Some patients in specialized therapeutic areas may have been initially concerned about going to a healthcare facility or physician clinic to receive treatment via an injection or infusion, but data suggests a recent rebound. Additionally, the government's stimulus packages provided short-term relief from an economic standpoint, and some employers also allowed newly laid off workers to maintain health insurance on a short-term basis. However, the unemployment assistance afforded in the federal stimulus ran out in July, and the outlook for a fourth stimulus remains uncertain.

Without a clear end in sight for the pandemic, the economic impact – and thus the demand for financial assistance to help support patients accessing their prescriptions – could still surge in the future. As such, manufacturers should proactively prepare for an increase in financial need from uninsured, and even underinsured patients, and explore ways to enhance patient access in the challenging months ahead.

To prepare for the various scenarios that could play out in these rapidly changing times, manufacturers should

conduct a series of financial exposure analyses that project patient demand and financial exposure for assistance programs. Exposure models project the financial needs of various patient populations based on current and emerging trends in the greater healthcare landscape. Some manufacturers have this capability in-house, but there are a limited number of external patient-support partners uniquely positioned to model the impact of developments within the broader landscape on patient and copay assistance programs via an exposure analysis. These patient-support partners model various contingencies and scenarios to determine how manufacturers should prepare, and to identify whether additional resources are needed to meet that demand.

Such financial analysis is particularly important for specialty areas that require high-touch products and treatments, such as oncology, immunology, and multiple sclerosis. If these patients discontinue their treatment regimens, they are at high risk of becoming more gravely ill and may face greater financial challenges in the future as a result of a worsening condition. At the same time, manufacturers risk losing these patients if their previous therapy regimen is no longer effective following a lapse in treatment.

Pharmaceutical manufacturers generally use patient support programs to help them manage affordability and access obstacles. In our current environment, it is critical to reassess patient needs and adapt accordingly. Manufacturers must consider how to adjust their current patient support programs to appropriately reach a wider swath of patients and effectively address the new and unique challenges facing the industry. This type of adjustment in the age of COVID-19 may include expanding the typical income eligibility criteria required for a patient assistance program (PAP) or minimizing the documentation to apply for PAP support.

"Manufacturers risk losing these patients if their previous therapy regimen is no longer effective following a lapse in treatment."

Manufacturers should also consider further enhancing their provider portals. Before the pandemic, patients may have applied for financial assistance via a patient support program in the physician's office. Today, with fewer patients making in-person visits to their providers, manufacturers should consider establishing a provider portal that is accessible through the support program website. The portals allow providers and their office staff to enroll patients into support programs and review status updates for select patients.

Regardless of the changes that manufacturers may implement to their programs, it's imperative to educate providers and their office staff that such programs exist. Recent studies have shown that only 40 percent of healthcare providers are "very aware" of manufacturer-sponsored patient programs, and less than one in five patients are aware of the support services available to them (1). With the pandemic reducing in-person interactions with doctors, this gap in education is at risk of widening.

Field reimbursement specialist (FRS) teams, who assist providers in navigating complex challenges, play a critical role in driving awareness for manufacturers' patient support programs. FRS teams offer robust tools and resources to help providers manage patient access and reimbursement hurdles, which have become increasingly important given nearly 50 percent of provider offices at the time of writing have furloughed staff (2). In addition to raising awareness for the programs themselves, FRS teams also ensure providers remain up-to-date on any adjustments or changes to manufacturers' programs, so they can make the most appropriate recommendations to patients.

To accommodate the shelter in place and social distancing policies implemented at the outset of the pandemic, interactions between FRS teams and providers have largely transitioned to a virtual support model, leveraging a mix of web-based and phone engagement. Given the accessibility of virtual platforms, this trend may continue to some degree even after the intense period of social distancing ends, but more provider education, in whatever form, will continue to greatly benefit patients.

As the long-term impact of the COVID-19 pandemic continues to unfold in the months ahead, manufacturers have a responsibility to respond to the changing needs of their patient populations. Actively preparing for an uptick in uninsured patients, anticipating a shifting demand for patient and financial support, and evolving interaction strategies with healthcare providers should help companies successfully position themselves to maintain patient access and ensure affordability of therapy.

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The Pandemic Diaries

We ask medicine makers around the world to tell us how their professional and personal lives have changed over the course of the COVID-19 crisis

By Don O'Callaghan, Vice President European Operations at West Pharmaceutical Services

COVID-19 is a unique and challenging time marked by the need for unprecedented leadership and navigational skills for all of us. As a leader, I truly never expected to be in a situation where I was forced to activate the company's Regional Pandemic team – it's something you plan for but hope to avoid. But I have been hugely inspired by our teams at West and everyone's ability to stay focused during these difficult times. Our employees have demonstrated enormous strength of character and have been working at a steadfast pace to rally and deliver to the cause. I feel my colleagues and I shoulder an enormous burden to respond to the global need brought about by COVID-19. We are committed to supporting solutions, including both the development of much needed treatments and vaccines, and ensuring supply of the critical components and devices needed for the healthcare industry.

From the outset, my top priority has been – and will continue to be – the health and safety of West's team members and their families. This pandemic has had an unprecedented impact on our communities. Our families have lost friends and loved ones, and we've faced disruption in every aspect of our lives. Navigating successfully through challenging times has given me a unique insight into our teams and shown how strong we are when we support one another.

I'd say the pharmaceutical industry's response to the pandemic has been exceptional. I believe global collaboration is vital in the treatment and cure of COVID-19. New relationships and ways of working have been forged with business customers within the industry and my hope is that the work we do here at West will go some way to helping with the development and delivery of new treatments and vaccines for COVID-19.

By Amélie Boulais, Vaccine Platform Marketing Manager at Sartorius

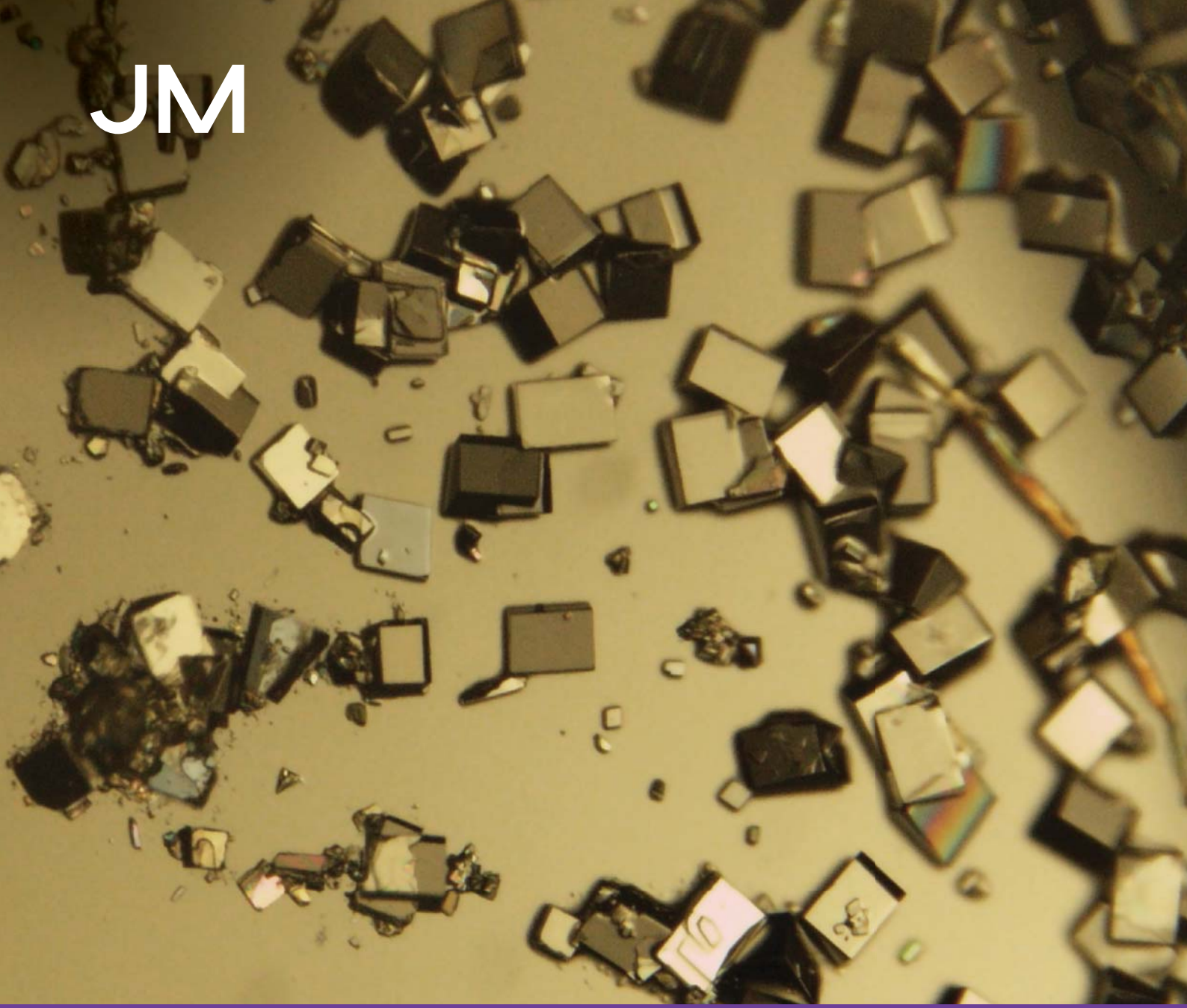
At the conferences I attended in the past, a topic that came up frequently was, "Are we ready for a pandemic?" The answer now is obvious: no. We were not ready enough.

As a supplier to the biopharma and vaccine industry, Sartorius has witnessed the impact of COVID-19 on our sector first-hand, and we are seeing reallocation of biopharmaceutical pipeline priorities in record time. On the one hand, we are working with scientific teams globally to provide technology to help them develop their SARS-CoV-2 vaccine candidates at unprecedented speed. On the flip-side, many companies are slowing down development as their clinical trials are put on hold. And that means readjusting priorities, product roadmaps, and manufacturing capacities.

For me, the crisis is shining a light on why organizations such as the Coalition for Epidemic Preparedness Innovations (CEPI) are vital in today's vaccine industry landscape. It also highlights the value of disruptive vaccine technologies, such as mRNA and viral vectors; I am incredibly interested in seeing how these potential game-changers perform in clinical trials.

Despite the underlying competitive spirit among biopharma companies to be the first to create a vaccine, I believe this pandemic demonstrates the importance of collaboration among different industry members. Many of the front runners for a SARS-CoV-2 vaccine candidate come from diverse teams that are benefitting from pulling together complementary areas of expertise. And this includes small biotechs or universities that have developed promising candidates working alongside established vaccine developers, with a well-rounded history of managing clinical trials and regulatory knowledge. These companies, in turn, are collaborating with contract manufacturing organizations, life science suppliers, and funding organizations. The real challenge is the speed with which vaccine developers are trying to create COVID-19 vaccines: 12–18 months instead of 10 years. And that is where great teamwork is proving vital.

From this pandemic, we are learning that we must set up protocols to facilitate communication between vaccine developers, vaccine manufacturers, and regulatory bodies. We must facilitate the dissemination of the right information at the right time to the right people. We also need to retrospectively analyze which parts of existing processes failed (if they were in place) and strengthen industry associations, such as the CEPI, as well as non-profit organizations, and expert groups working on pandemic preparedness. We need to fund them properly and give them more power, as it will help us all be better equipped to deal with any future pandemics.



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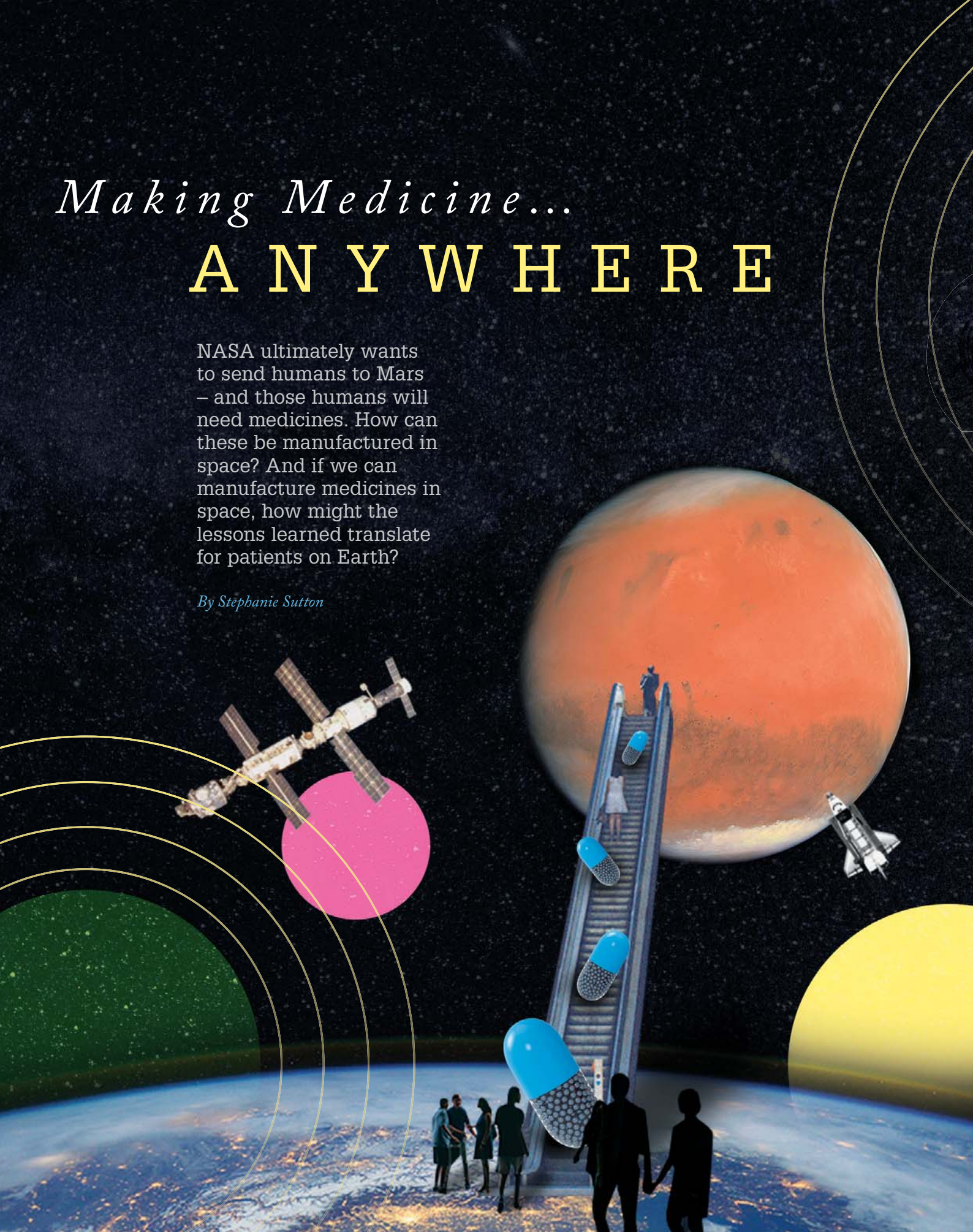
Making Medicine...
ANYWHERE

NASA ultimately wants to send humans to Mars – and those humans will need medicines. How can these be manufactured in space? And if we can manufacture medicines in space, how might the lessons learned translate for patients on Earth?

By Stephanie Sutton



A Grueling ENVIRONMENT

By Phil Williams

The altered environment of spaceflight causes changes in many biological processes that have evolved to function in the 1G, radiation-free, temperate, saline environment of Earth. The immediate change to the body is caused by the environment of microgravity, where astronauts are in constant freefall as they orbit the globe. This environment causes redistribution of fluids in the body, in particular the blood, which is no longer pulled towards the feet and away from the head. The body compensates for this unnatural pooling in the upper half of the body by then reducing the volume of the blood. These changes in fluid distribution and blood volume all cause immediate changes to pharmacokinetics/pharmacodynamics (PK/PD). Studies on the SpaceLab (the laboratory that flew in the bay of the Space Shuttle), for example, have shown that the rate of absorption (measured in saliva) of paracetamol and scopolamine/dexedrine from tablets were double after one day of space flight, and almost halved after two. Longer term changes caused by microgravity include muscle atrophy, insulin receptor desensitization (astronauts can be clinically diabetic after 30 days of spaceflight), retinopathy, and decalcification of bone (and the consequent deposition of calcium elsewhere, often as kidney stones).

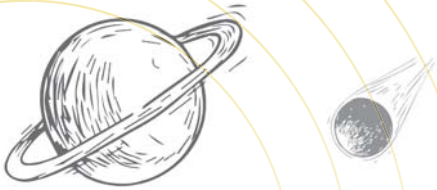
It has also been shown that stem cells change in microgravity. They tend to remain undifferentiated in flight, but they differentiate on return to Earth along one lineage far quicker than normal. Bacteria are also shown to behave differently. Whether due to changes in the mechanics of membranes evident in parabolic flight or cell surface receptor recruitment or other factors, bacteria have been shown to be more resistant to antibiotics and, for other reasons, antibiotics are also less effective.

With changes to bacteria, there are also changes to the gut microbiome. Enzyme activity has been shown to be affected, meaning that food and medicines are absorbed and processed differently during spaceflight. With the now-known link between the gut and the brain, and the link between the state of the microbiome and mental health, there are many interlinked and complex issues that need to be researched and understood when it comes to long-term spaceflight. And issues around mental health will only be compounded by the obvious pressures of confinement, social isolation, stress, and changes in circadian rhythm.

All of these issues, and more, come to the fore when considering a mission to Mars. Such a mission, described by NASA's Design Reference Architecture 5.0, on which Andrew Weir wrote the book 'The Martian,' would be around three years with a crew of six. It has been estimated that the chance of serious illness or death in an activity such as spaceflight is 0.06 per-man-per-year. The chance of such an incident in one of six crew in their three-year mission to Mars is 67 percent. There is a 20 percent chance that half the crew will suffer. We must find a way to treat these explorers if such a mission is to take place. They cannot take every medicine with them on the journey.

Bringing things closer to home, the often dramatic and largely unpredictable rapid changes to PK/PD on spaceflight could produce real and current problems in the area of space tourism. For paracetamol, a doubling of the rate of absorption and maximum plasma concentration after a few hours of flight is not a huge problem. But if the astronaut took a drug with a narrow therapeutic window, then such a change could be fatal. Until now, astronauts are selected based on their physical and mental fitness (and on the payroll of national governments). But with the advent of space tourism, where the financial drivers and considerations differ, the considerations of medication become greater. Who will license? Who will authorize? Who will prescribe? Who will provide the medical information for space medication? This area – although not covered in this feature – is something that my colleague, Li Shean Toh, at the University of Nottingham, is developing.

Phil Williams is Professor of Biophysics, Director of Research and Knowledge Exchange, School of Pharmacy, at the University of Nottingham, UK



The ASTROPHARMACY *Concept*

A system for making medicines on demand

Lynn J. Rothschild is a senior research scientist at NASA's Ames Research Center with a keen interest in evolutionary biology, but more recently she has been involved in creating an "astropharmacy" system that can produce biologic drugs on demand (1). Her work combines pre-programed cells in spore form, genetic engineering, and a small volume system adapted from standard laboratory protocols.

WHERE DID THE ASTROPHARMACY CONCEPT COME FROM?

Around 15 years ago, our Center Director at the time asked me to start a program on synthetic biology, with the idea that it could potentially be a game-changing technology for space exploration.

I met Phil Williams, a professor of pharmacy at the University of Nottingham, when he came to visit a postdoc student at NASA Ames. He was very interested in the work we did, and we came up with the idea of "astropharmacy" – combining my work with the pharmacy field to solve the challenge of delivering pharmaceutical care in space.

WHAT ARE THE UNIQUE CONSIDERATIONS FOR SPACEFLIGHT, PARTICULARLY IN TERMS OF MEDICINES?

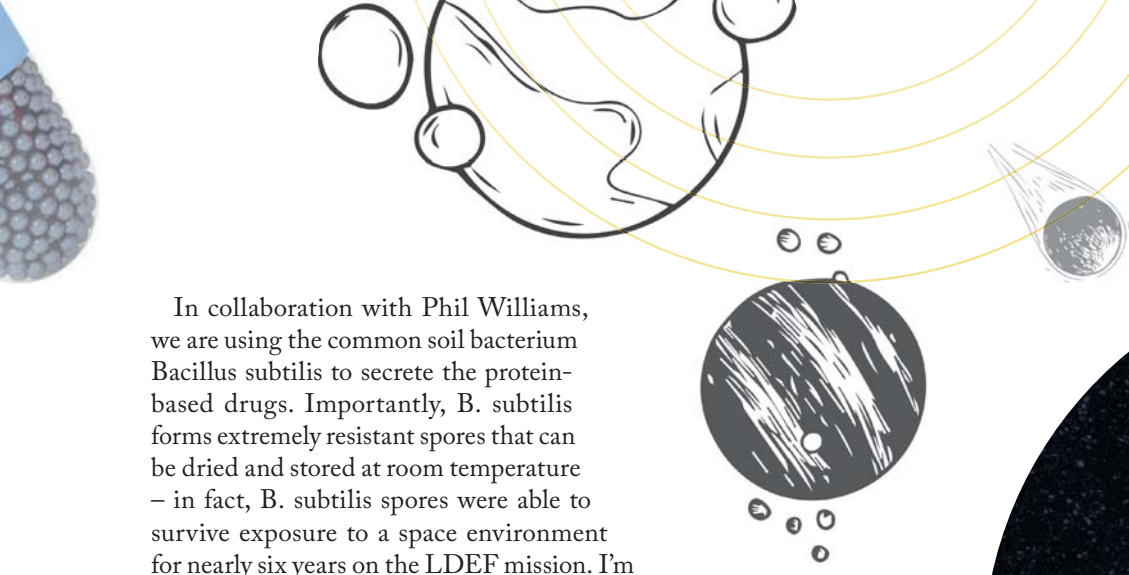
It is extremely expensive to launch a spacecraft. A large part of the spacecraft is jettisoned in the first few minutes after take-off because of the sheer amount of fuel required to escape the Earth's gravity. Saving mass and volume is critical, so astronauts must carefully consider what they take with them. In terms of an astronaut's health, there are significant medical tests and a quarantine period before someone is allowed to go into space. Health should not be a problem on short-term missions and astronauts are closely monitored. If there was a problem, the astronaut could return to Earth, or a medication could potentially be sent up.

But what about long-term missions? There are plans for a long-term human presence on the moon and, eventually, to send humans to Mars. With current technology, it would take around six months to reach Mars and the astronauts would have to stay a year and a half for the planets to realign to minimize the journey time home. For such a long trip, you cannot possibly pack every potentially useful medicine. It would take up too much mass – and most medicines also have a limited shelf life, which would render them useless part way through the journey.

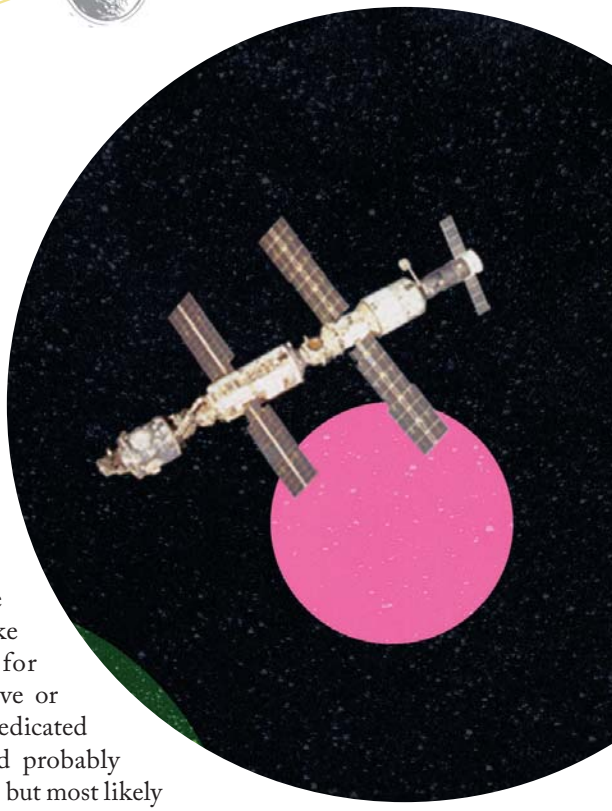
"You cannot possibly pack every potentially useful medicine. It would take up too much mass."

When NASA put out a call for projects for making drugs on demand, we decided to focus on biologics – and we now have funding from the NASA Innovative Concepts Program. Biologics are extremely expensive and have a very short shelf life, even with refrigeration. However, many of the medical problems that astronauts could potentially face could probably be effectively treated with biologics.

From the point of view of a bioengineer, protein-based drugs are easy to make. If the DNA has the right coding mechanism then it should be possible to get the organisms to synthesize the right protein. Initially, we've been working on non-glycosylated biologics, but in principle we should also be able to figure out ways to glycosylate the proteins, and to engineer cells with different metabolic pathways so that we can make other things too besides protein-based drugs.



In collaboration with Phil Williams, we are using the common soil bacterium Bacillus subtilis to secrete the protein-based drugs. Importantly, B. subtilis forms extremely resistant spores that can be dried and stored at room temperature – in fact, B. subtilis spores were able to survive exposure to a space environment for nearly six years on the LDEF mission. I'm actually working with these spores on another mission, PowerCell on Eu:CROPIS – and they are working beautifully! B. subtilis is already used as a platform for bioengineering, so a lot of the relevant lab tools already exist. Essentially, we just need to program the bacteria, put them in spore form, and then they can be sent into space – potentially on punch outs on a piece of paper, though we are exploring other approaches too. Once reconstituted, they can be used to produce the protein. We are also working on approaches to purification.



WHAT TYPE OF EQUIPMENT WOULD ASTRONAUTS NEED TO TAKE INTO SPACE TO PRODUCE MEDICINES ON DEMAND?

To answer this question, I'll direct you to students who worked on the International Genetically Engineered Machine (IGEM) competition (2). I've been working on the astropharmacy system with a team of students from Brown University and Stanford University – and last year we also had some wonderful students from Princeton University. One of the Browns students is also working with me for his Masters – and, incidentally, he is specifically interested in taking the technologies into the pharmaceutical industry. Currently we also have an undergraduate from Yale working on the manufacturing technologies.

The students are working on technologies and approaches for diagnostics, drug production and drug purification – and have come up with technologies for a synthesis system, drug expression chamber, and a purification platform. I've been very firm with them that the technology needs to be as small and as simple as possible! Astronauts will want an easy system – preferably something that works at the press of a button. Right now, we have a lab system that requires an external pump and various other components, but I am pushing for us to use microfluidic systems. I can't give too much away on this at the moment… come back to me in a year! But I will say that we are aiming for something the size of a wallet that doesn't require an external pump. It will, however, depend on the size of a crew. If we need to make medicines for a crew of five or ten, then a dedicated pump would probably be necessary, but most likely medicines will only be required for one or two individuals. If medicine is needed for something chronic, then we envisage that an astronaut could set up a production day once every three months or so to create a backlog. Other medicines can just be made on demand.

WHAT IMPLICATIONS DOES THE ASTROPHARMACY HAVE FOR PATIENTS ON EARTH?

I really believe that a lot of what we do at NASA and in the space industry ultimately has applications for Earth. Pharma companies focus on producing a large number of doses with a high profit. With our system, we have the opposite situation in that we can only produce very few doses – but this is exactly what is needed for some medicines, such as orphan drugs. We've had pharma companies approach us before about our work because they are specifically interested in orphan drugs and making personalized medicines on demand.

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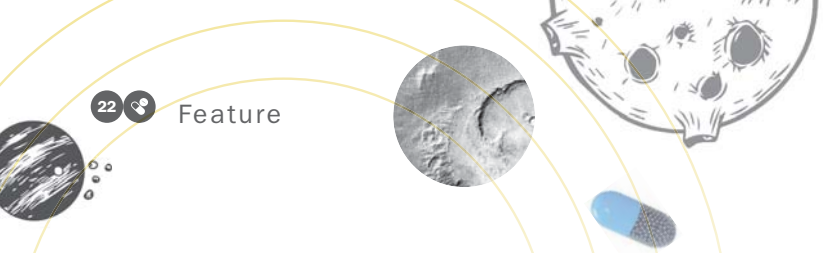


Down to EARTH

Aiming for technologies that can make medicines in space or on Mars can also help us with problems closer to home, such as challenges with cold chain and getting medicines to remote locations

With Phil Williams

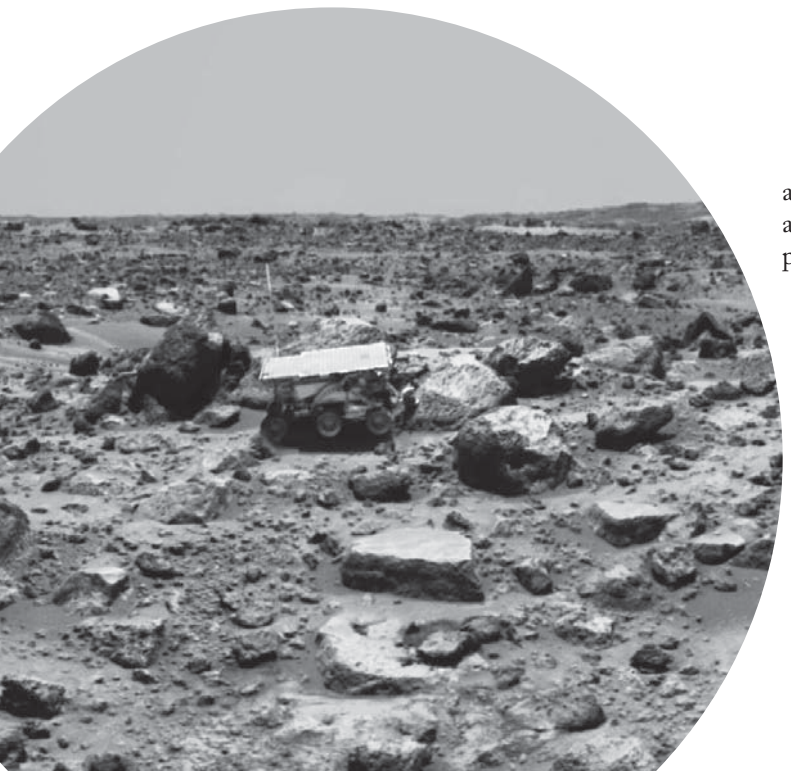
The excitement of working on projects that will enable human exploration of Mars is huge. I don't think we'll see people landing on Mars during my lifetime, but the greatest driver for me is knowing that if we can maintain and restore the health of explorers on Mars, then we can do it anywhere – in a hospital, on a nuclear submarine, in the Antarctic, or in a remote community in South America. Making a medicine on site and on demand, using resources that can be sourced locally – and ideally that are waste products from something else – would solve issues with cold chain. Cold chain supply accounts for roughly one percent of the total pharmaceutical market. Although one percent isn't much, the numbers add up fast when you consider that the pharmaceutical market is worth well over US$1 trillion… and the vast majority of cold chain products (60 percent) are transported by air. If we can get rid of centralized manufacturing and make medicines for individuals where and when they need it, there will be huge advantages in terms of cost and the environment – as well as for patients, who will get the medicine they need tailored to them.

"An on-demand approach to drug manufacturing could completely change how we make medicine – and realize the ultimate goal of telepharmacy."

My group has done a lot of work with cell-free synthesis. From our work on in vitro evolution, we began exploring the use of synthetic biology to make proteins. Here, we take the machinery that a cell uses to make proteins out of the cell and put it in a test tube. With a DNA synthesizer, it is possible to make DNA strands of any sequence. We can give the DNA that encodes a particular protein to the cell machinery – which then produces the desired protein. Our cell-free protein synthesis method uses the machinery from an extremophile (Deinococcus radiodurans), combined with microfluidics and novel protein storage and reconstitution ideas. The project is funded by the UK's Engineering and Physical Sciences Research Council (EPSRC), through their Adventurous Manufacturing program.

Once the protein is produced, it has to be formulated into a deliverable therapeutic. To do this, we are working with 3D printing experts. Some of my colleagues at the University of Nottingham – Clive Roberts' group – are pioneers in additive manufacturing and in particular of pharmaceutical formulations. We are considering a variety of ways in which 3D printing can be used for formulation of the on-demand-manufactured drug, such inhaled drug delivery or dissolvable microneedles.

An on-demand approach to drug manufacturing could completely change how we make medicine – and realize the ultimate goal of telepharmacy, where a pharmacist or medical practitioner can transmit a particular drug and its formulation over any distance. Once the technology is in place to synthesize and formulate the drug on demand, all that is required is a set of instructions that tell the system how to make the drug (the DNA codes) and formulate the



resulting protein into an appropriate dosage form (the printer instructions), with the correct release profile. We're talking about a digital file that could be sent across continents… or across the solar system.

Theoretically, we could separate the drug discovery process from manufacturing and distribution. It would be possible for a drug discovery company to release a drug without having to go through the process of manufacturing and transporting it. They would just release the software or instructions for the drug, which could be downloaded across the globe to make the medicine. We're not at that point yet, of course.

Biologics are considered the future of most medicines – and are the ones with the most demanding cold chain requirements – but there will also always be demand for small molecules too. We're also looking at how to make small molecules the way nature does by using cell-free synthesis to make enzymes that can convert one material to another. It's all early work and baby steps but, ultimately, we envision a system that can make protein therapeutics, and also proteins that can be used to make more molecules.

SPORES FOR SPACE

The project with Lynn at NASA and others builds on the cell-free synthesis method and uses spores, which have been shown to survive the environment of space outside of the ISS, to house the cell machinery. The idea is to create a system that allows astronauts to create biopharmaceuticals on demand. We are using a number of protein-based therapeutics as exemplars – a thrombolytic (stroke is a risk factor of space flight), a hormone for osteoporosis prevention (decalcification

Extraterrestrial RISK

What biosecurity risks do exo-microorganisms pose? Neil Gow, Deputy Vice-Chancellor for Research and Impact, and a professor of microbiology at the University of Exeter, UK, and Mihai Netea, a professor at Radboud University Medical Center, the Netherlands, mulled the idea while walking on the beach at a scientific meeting in the Caribbean – and devised two potential studies on how to address the risks. The first of those studies was published earlier this year (1): "A Weakened Immune Response to Synthetic Exo-Peptides Predicts a Potential Biosecurity Risk in the Retrieval of Exo-Microorganisms."

Discussing the work at an astrobiology conference in Seattle in 2019, Katja Schaefer, lead author on the study, discussed the field of exo-immunobiology (originally introduced by Netea) – where the human immune system encounters either a completely alien microorganism, or Earth organisms that have been adapted to space environments. How would the immune system react? And would it even recognize the organisms to elicit an immune response?

Exo-microorganisms are not just a risk for those exploring space – they could be brought back to Earth during sample retrieval from exoplanets or moons, for example. Schaefer, Gow, Netea, and their co-authors believe that exo-microorganisms with distinct proteomes may present immunological challenges. Their study tested the mammalian immune response towards protein antigens containing two amino acids: isovaline and α-aminoisobutyric acid. Both are extremely rare in earth organisms, but have been identified in abundance in chondrite meteorites.

"My background actually lies in fungal pathogens, but when I started working with Neil Gow, he told me about his provocative ideas involving amino acids on

meteorites – and it was interesting! We decided that I would start it as a side project to my main work," says Schaefer. "Other papers have discussed the characterization of amino acids from meteorites, but to find out how they'd affect the immune response, a peptide was needed. I didn't have an immunological background, so we brought in other collaborators. Once we had the peptide, we isolated immune cells from mice and measured the effect when they were exposed to the peptide."

The result? The peptide was recognized by the immune system, which led to an immunological response, but T cell activation and proliferation were both significantly reduced compared with exposure to common peptides on Earth.

What does this mean for humans? It's very difficult to say, but peptides or organisms made up of different amino acids to those on Earth could pose an immunological risk. "There are many other questions that we can also explore, such as why the immune response was low, what enzymes and processes are involved, and whether it is possible for the mammalian immune system to produce antibodies in response to the peptides," says Schaefer.

The risk could also be greater for astronauts. Conditions in space can also change how the immune system works. Astronauts are exposed to very extreme environmental stresses, including microgravity, radiation, and poor nutrition – which can result in a weakened immune response, including reduced cytokine release and reduced T cell function (2). "This is already in effect without exposure to a pathogen – and also remains in effect for some time after the astronauts have returned to Earth," explains Schaefer. "It would be interesting to do experiments with the immune cells of returning astronauts to see how the immune response changes when exposed to these rare amino acids. We also want to look at how the properties of terrestrial microbes could be altered by growing on exo-substrates. I'm also interested in the fact that different sugars have been found on meteorites – and, recently, a peptide. This is a vibrant area of research."

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of bone), a toll-like receptor 5 agonists (radiation protection), and G-CSF (for neutropenia).

Once you leave Earth, there is no ionosphere for protection and the conditions are extreme. Solar radiation is very damaging, and there are also extremes of hot and cold. With Lynn, we discovered that spores are a very robust container for cell machinery and are resistant to the damage of space. Spores housed on the outside of the International Space Station for around three years were still able to regenerate and produce proteins. Nature never ceases to amaze me – and this is also why a lot of work has looked at extremophiles that have evolved in extreme environments, such as hypothermal vents, the Antarctic, or the bottom of the ocean. Now, we are combining spores with microfluidics as a way to handle and reconstitute them effectively. For the platform, you'll be able to push a button to reconstitute the spores and then they will start protein production.

As well as ensuring the spores can survive in space, we also need to consider the technology that will be used to make the platform. It must be a self-contained unit, so that if something goes wrong it doesn't cause a cascade failure that affects the spacecraft. It must also be robust, and capable of self-monitoring and correcting errors. The people that are using it aren't going to be pharmacists or biochemists, after all.

And then we need to consider the purity of the protein therapeutic that is produced. When it comes to consistent quality and purity for biopharmaceuticals, even big pharma companies can struggle. Something that is in our favor though is that we are only making relatively small amounts of material, which makes purification much easier. When purifying a large batch of product, at times it can be like looking for a particular needle in a pile of different but ever-so-similarly looking needles. We are still working on purification methods but, ultimately, we hope to incorporate an automated quality control function into the system. We are very interested in antibody fragments and nanobodies because they can be produced using the cell-free system. We would express the protein we want, and also the antibody for that protein, with the latter being used to separate out the protein. Both protein and nanobody would have to be folded correctly and functional for the separation to work, and in this way only correctly folded and functional biologics would be outputted from our system. It is early stage, but we are making progress.

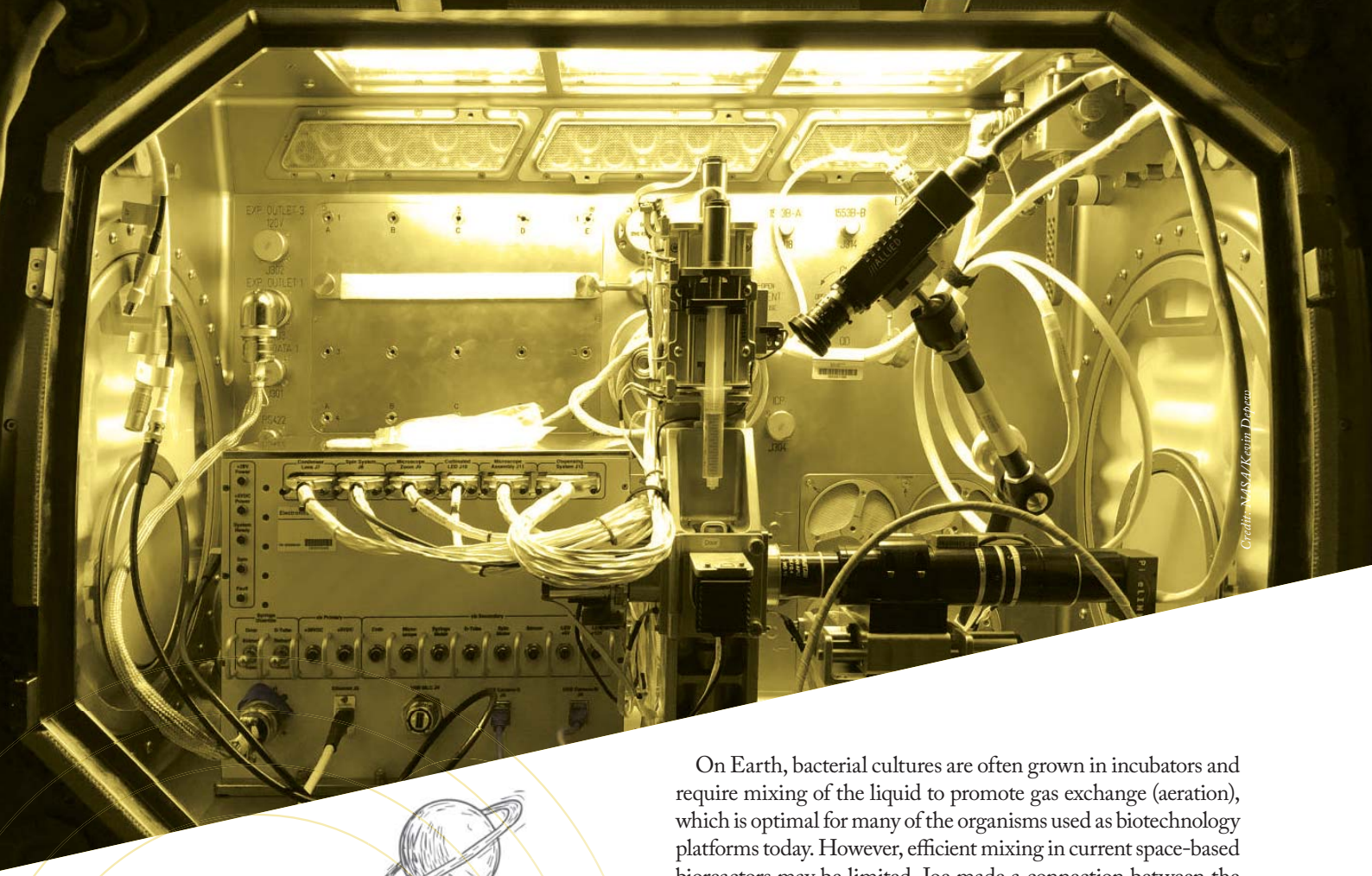
A BOLD NEW FIELD

Our astropharmacy field is growing and every corner we turn opens up many new directions. It's a very exciting field to be working in. We currently have seven PhD students working on a variety of projects, including:

- On-site, on-demand manufacture. Linked to the EPSRC project mentioned earlier, this project is studying various extremophiles as potential sources of environmental-tolerant cell-free protein synthesis.
- Drug delivery from halophiles. Exploring the particular and unique properties of halophiles, and whether we can reverse engineer novel drug delivery vectors based on their membranes.
- Cold plasma food processing. The nutritional requirements and ability to absorb nutrients of an astronaut changes in time. We are exploring the use of processing technology as methodology to modify the physical and nutritional content of food for personalized care.
- Bacterial/immune system crosstalk. It is known that both bacteria and the cells of the immune system change in microgravity. We are studying any interlink between the behavior of these two systems to research potential new methods to control infection and moderate disease.
- Insulin receptor dynamics and restorative treatment. Insulin receptors in muscle shutdown in spaceflight after a month. The same happens to immobile patients after a few days. This project is researching the biochemical processes that regulate receptor activity, and looking at potential pharmaceutical therapies and engineering solutions prevent or restore activity.
- CubeSAT design. Ultimately, research into how to make medicines and treat people in space needs to be done in the environment of spaceflight. Here, we are developing a flexible platform for astropharmacy experiments, based on a CubeSAT design. We hope to fly the first Astropharmacy CubeSat in February 2021.

"In my view, astropharmacy is a new way to teach people to solve problems."

The enthusiasm of the students is inspiring – and by focusing on the extreme problem of supporting life on Mars, I believe that we will, as a consequence, come up with many new solutions and approaches that can also benefit patients on Earth. In my view, astropharmacy is a new way to teach people to solve problems. It's not about solving the particular problem, but translating problems to new environments. Because when you look at a problem from a new angle or in a new environment, you can often find new insight.



Bringing BIOREACTORS *to Space*

Is it possible to design a bioreactor that can function in microgravity?

With Richard Bonocora, senior lecturer at Rensselaer Polytechnic Institute

One day, a student, Joe Adam, who had previously been in my class, came to ask if I still had the bacteria we had worked on that expressed green fluorescent protein. When I said yes, he asked if I would like to send them into space.

He was working on a project with Amir Hirsa, a professor of Aerospace Engineering at Renssaeler, involving the ring-sheared drop (RSD). The RSD was developed to study the flow within liquids without the constraints of solid walls, something that can only happen in the absence of gravity. In microgravity, free liquid naturally takes on a spherical shape and it is this property of liquids that the RSD exploits. The edges of two cylinders (contact rings) touch the drop and use surface tension to hold the drop in place. One ring then rotates while the other is stationary, producing flow and mixing throughout its volume through the action of surface shear viscosity – all without the need for a solid container.

On Earth, bacterial cultures are often grown in incubators and require mixing of the liquid to promote gas exchange (aeration), which is optimal for many of the organisms used as biotechnology platforms today. However, efficient mixing in current space-based bioreactors may be limited. Joe made a connection between the fluid dynamics technology that Amir was developing and the biological principles he learned in my class, and came up with the idea of using the RSD as a bioreactor to more efficiently aerate and grow microorganisms such as E.coli in space. These microorganisms could be used to help astronauts produce protein-based medicines that may be necessary during long-term space exploration. Currently, inhabited space missions are limited to low Earth orbit (LEO) on the International Space Station. Basic human necessities, including pharmaceuticals, food, and water, are provided by frequent resupply missions. The need for pharmaceutical production becomes important as the missions become more adventurous and spacecraft travel past LEO to the Moon, Mars, and beyond. I was intrigued – and thus began my interest in the field of space microbiology.

As with other bioreactors, the RSD will require a motor and a harness to secure it during space flight, but since surface tension is doing all the heavy lifting regarding the liquid, there is no additional container weight. Furthermore, problems of biofilm formation and the resulting biofouling that have been observed on previous space missions are substantially mitigated as only contact rings touch the culture.

My collaboration with the team began a few years ago. Since then, the RSD has been installed on the International Space Station (2019) and is being used to study the formation of protein clusters like those found in brain tissue in neurodegenerative diseases (1).

We recently reported on how we used a ground-based analogue of the RSD called the knife-edge surface viscometer (KEV) to evaluate the feasibility of growing microorganisms in microgravity and the RSD (2). The RSD only works in microgravity, which makes it difficult to test on Earth! However, tests with the KEV, which also uses surface shear viscosity to produce mixing, show that it is a viable method of growing E. coli. In addition, recombinant protein expression was comparable to using standard growth methods. We're now planning to do tests to see if the RSD can successfully hold drops with living bacterial cultures during short bursts of microgravity on a parabolic flight (also known as the Vomit Comet) (3). I'm positive that we will see some good results!

I am now working on optimizing microorganisms for space, by selecting or engineering the new organism(s) for producing biologics in space with improved functions such as growth rate and protein production. At the moment, we are focusing on improving resistance to radiation. As missions extend deeper into space, exposure to galactic and solar radiation will increase. Astronauts will need adequate shielding to protect them from such exposure. Microorganisms used to produce biologics will also need shielding. However, we are interested in reducing the amount of physical shielding needed by microorganism biofactories. There are microorganisms that have extreme resistance to radiation. We are investigating how to harness these abilities and put them to use with more biotechnologically amenable species to create a "cellular shield" that protects the contents of the cell, namely the desired biologic.

In essence, this will transfer the shielding burden from the spacecraft to the cellular factory and will allow more shielding mass to be devoted to the astronaut cabin. I liken this to the difference between the insulation needed in a family's home as compared to that needed for their garage. Garages are always cold or hot, but you don't have to live in them!

I am fortunate to be working at Rensselaer with so many bright students like Joe who have so many great ideas. I am also fortunate that Rensselaer has an extremely supportive collaborative environment. Fluid dynamics and engineering expertise lies with Amir, Joe and Shreyash Gulati (another member of our team who provided critical analysis to our KEV work). My role lies on the microbiology side. I believe collaborations like ours that combine different disciplines are what's important to drive science forward.

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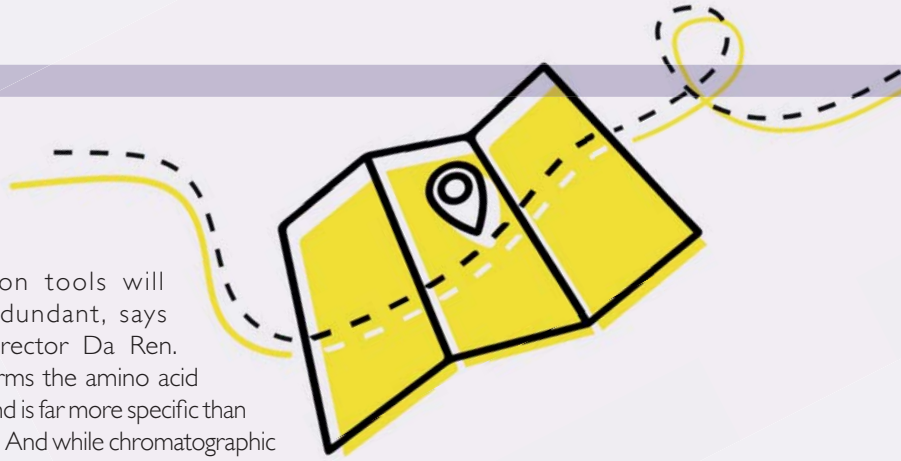


Mapping Out MAM

Amgen has brought the Multi-Attribute Method (MAM) into the mainstream, but what's next for this analytical workflow – and for biopharmaceutical QC?

Da Ren is Scientific Director, Jette Wypych is Executive Director, Attribute Sciences, and Ting Song is Senior Scientist, all at Amgen, Thousand Oaks, California, USA.

In the biologics industry, it sometimes seems like the only constant is change. Consider how the cumbersome, laborious mass spectrometers of the 1980s have evolved into sophisticated protein analysis tools. Today's instruments, says Ting Song, a Senior Scientist at Amgen, can even analyze binding of a drug to its target. Amgen now has taken mass spectrometry into the cGMP environment – so what changes should we expect next?

The new normal

If you want a hint on what's next for MAM, think about how quickly SDS-PAGE clipping assays were replaced by electrophoresis. "Electrophoresis will in turn be displaced by MAM – not just CE-SDS but also capillary IEF," states Executive Director of Attribute Sciences Jette Wypych. "MAM is not intended to be complementary to existing assays – it is a replacement." She lists QC techniques likely to be less prominent in the future: certain chromatographic methods for assessing amino acid modifications, glycan mapping techniques, ion exchange chromatography, hydrophobic interaction chromatography, and standalone peptide mapping methods with UV detection.

Similarly, antibody-based identification tools will become redundant, says Scientific Director Da Ren. "MAM confirms the amino acid sequence – and is far more specific than ELISA assays." And while chromatographic methods may detect charge variants, only MAM elucidates the molecular basis of the variations. "It doesn't just alert us to a peptide modification, it defines the precise site of the modification," notes Ren. Consequently, MAM allows detailed assessment of the relevance of such events to drug safety and efficacy.

Growing regulatory endorsement

Amgen's quality focus inevitably led the team to concentrate on monitoring and control of critical quality attributes (CQAs) in biologics manufacture. "It's all part of the quality by design (QbD) approach," says Ren. "MAM allows us to fully understand the product and to control its quality attributes throughout the development and manufacturing process." This, he says, is why MAM will have wide-ranging benefits to the pharmaceutical industry – and it also explains the increasing support for MAM from the regulators.

Wypych notes agencies' enthusiasm as well, especially after some adopted and gained experience with the method for themselves. But this didn't happen by chance – Amgen engaged major regulators early in the MAM development process. "At first, Amgen was a lone voice, but over the years we have slowly convinced the industry of the merit of MAM," says Wypych. And in 2017, Amgen – along with Just Biotherapeutics, Merck, Pfizer, Biogen, and Genentech – published a paper establishing that MAM was ready for QC application (1). "That was hugely uplifting!"

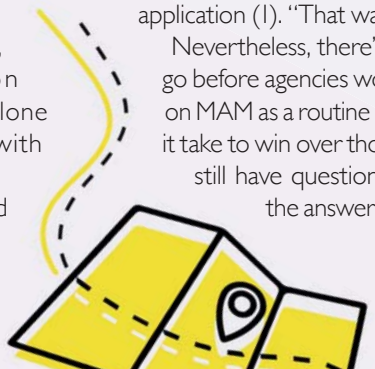
Nevertheless, there's still some way to go before agencies worldwide converge on MAM as a routine QC tool. What will it take to win over those regulators who still have questions? Wypych thinks the answer lies in providing full details of the MAM approach, operation and performance, including robustness, failure rates, and the standard criteria for "passing" a product with regard to CQAs. And she is confident of meeting the expectations of the regulatory bodies. "Eventually in the coming years, I expect MAM will be globally accepted as a replacement for conventional QC assays."

Ren emphasizes that MAM already fits very well with current regulatory thinking. "It fits exactly within the QbD paradigm." Furthermore, he emphasizes, MAM has satisfied all necessary ICH guidelines – for example, the current ICH Q2(R1) guidance – that pertains to analytical methods used in a cGMP environment. And that's why he expects to see continued uptake of MAM in the industry, and increasing acceptance by regulators worldwide.

"We have ambitious goals," says Wypych. "But look how far we've come in the last five years, and consider the growing momentum for MAM uptake – more and more companies are adopting MAM in their QC functions." But a key requirement, she says, is to make MAM sufficiently robust and affordable for adoption by all, including contract testing labs and import testing labs. The latter point, she says, is important for countries that require import testing, for example Russia, South Korea, and China.

Upgraded technical capabilities

In an environment as dynamic as the biologics industry, should we also expect MAM to evolve? Certainly, the Amgen team is always thinking bigger and better, and continues to refine MAM for various applications. Ren points out the enormous potential of this young technology, and outlines two broad areas of interest that he and his colleagues are currently addressing.



The first is automated sample preparation – an area of interest to many companies besides Amgen. Ting Song notes that automation in both sample preparation and data analysis would support the evolution of MAM into a real-time release and stability testing tool, compressing the testing cycle and helping manufacturers get drugs to patients in shorter time-frames.

In support of this endeavor, says Ren, Amgen has made significant investments aimed at extending their capabilities in automated data analysis: "The idea is that operators will simply put a sample into one end of the system and collect processed data at the other end – the intervening steps of sample preparation, sample analysis, and data analysis will all be automated."

According to Ren, advances in this area will likely need further close collaboration with instrumentation vendors. "We've already asked them to consider how we might collaborate to develop systems with higher levels of automation." In addition, says Ren, aspects of data analysis require improvement. "The methods used for integration of peaks haven't changed for decades – the time is ripe for application of artificial intelligence-powered data analysis; this could revolutionize the field and replace human analysts."

The second area of interest for Amgen is miniaturization. "Manufacturers will have to develop small-footprint mass spectrometers that are sufficiently compact and mobile to be moved around the manufacturing floor as operators require," says Ren. In addition, he believes that a range of software companies – not just the major vendors – will want to leverage the opportunities to develop solutions that support MAM in the QC environment. "This will result in growth in the currently limited number of vendors that can serve the compliance software field."

A virtuous circle

If any company can upend the bioprocessing environment, it's likely to be an archetypal biopharmaceutical pioneer such as Amgen. As Ren explains, Amgen's science-based culture and embedded values of agility and adaptability – present since its genesis – have remained with the company as it has grown into a major industry player. "Our values, together with our strategic focus on quality, explain why we continually seek to develop better products and thereby better serve patients," he says.

But there is another factor at play, according to Wypych: "To make a difference you have to be a risk-taker – while strongly committing to ensure compliance."

Amgen's desire to provide patients with the best possible options also informs the company's proactive engagement with regulators. "That won't change," says Wypych. "We've already facilitated a big positive change in many regulators' view of MAM, and we will continue to address any concerns as they are presented." Amgen's efforts have contributed to a sea-change in MAM uptake and enhanced the reputation as the developer of this novel technology. In other words, when quality is an intrinsic component of your core values, competitive advantage tends to follow.

To find out more, visit https://themedicinemaker.com/amgenmam

What should I look for when adopting MAM?

Instrumentation capable of providing data for attribute quantitation and new peak detection:

- high resolution (a measure for the width of a mass spectrometric peak – the higher the resolution, the narrower the peak and the higher the chances to distinguish ions that are very close in their detected mass to charge ratio [*m/z*] in a mass spectrum
- high mass accuracy (a measure of how close a detected mass to the theoretical mass of an ion is, provided as mass deviation in parts-per-million [ppm])
- reproducible isotope distribution (for peptide confirmation [requires reproducible measurements of ion intensities with high mass accuracy and high resolution])
- with highly reproducible chromatographic separation

Software that is:

- user-friendly (easy to use, automated data processing and reporting)
- allowing easy method transfer across instruments and sites
- robust and allows for reproducible result generation
- 21-CFR Part 11 compliance-ready
- capable of assuring data integrity and security (e.g., secure back-ups)

Systems that are:

- accessible for contract labs and for countries that must repeat manufacturer's release methodology (i.e., easy to use, affordable)

Vendors that:

- commit to long term support on instrument and software
- offer complete solutions pre-evaluated and optimized for user expertise level
- respond rapidly to service requests (minimize downtime)
- provide software training
- are open to collaborate on system/software optimization

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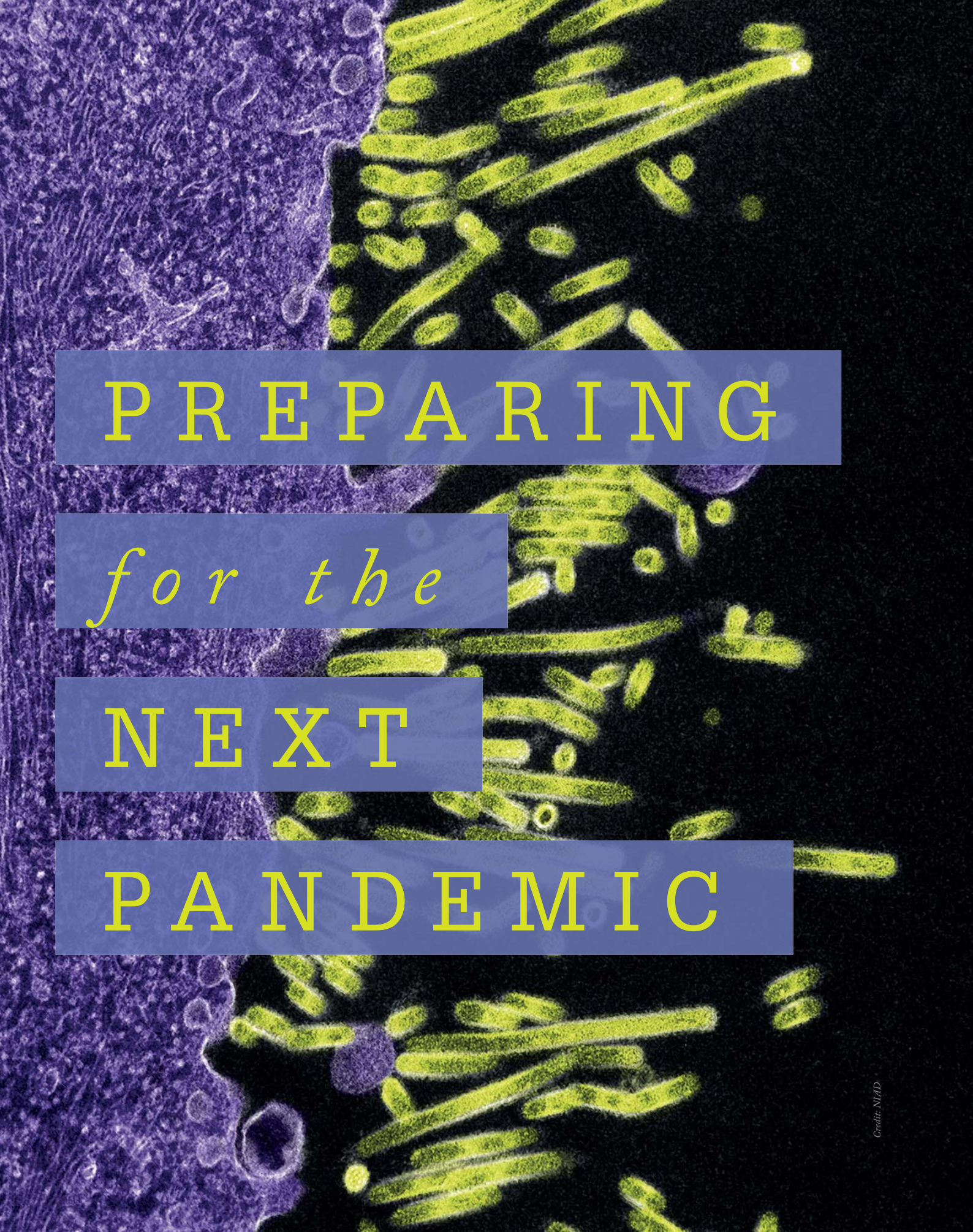
PREPARING
for the
NEXT
PANDEMIC
Credit: NIAID

Ever since the "bird flu" outbreaks of the mid-2000s, public health experts have been concerned about an influenza pandemic to rival the 1918 Spanish Flu. Now, blindsided by a less expected beast, can we transfer lessons on pandemic preparedness from flu to COVID-19? We caught up with Russell Basser, Head of R&D at flu vaccine manufacturer Seqirus to find out more about the past, present, and future of vaccine production – and how COVID-19 changes the outlook.

Your company has an interesting origin story…

Commonwealth Serum Laboratories – as it used to be known – was set up by the Australian government in 1916 as a public utility. At that time, it was hard for Australia to get access to modern medicines because they were developed and manufactured such vast distances away. The first big challenge for the newly formed CSL was the 1918–1920 Spanish Flu. The company was successful in producing what was referred to as a vaccine, but was actually an antiserum from patients with pneumococcal infection. CSL went on to produce insulin, penicillin, and vaccines for polio, diphtheria, tetanus, and whooping cough.

The first true vaccines for flu were actually developed in the US in the 1940s, based on the pioneering work of Australian Nobel prize winner Macfarlane Burnet, who discovered that flu could replicate in embryonated chicken eggs. In the late 1950s, CSL brought flu vaccination technology to Australia.

How have manufacturing technologies for flu vaccines evolved since then?

In the early days, the virus was grown in eggs, killed, and injected whole, but this caused some significant side effects. Soon, methods were developed to split the virus using chemical detergents and to purify it to leave only the viral proteins that give maximum immunity and minimum side effects. Even today, up to 90 percent of the world's flu vaccine supply consists of highly purified, inactivated viruses grown in eggs.

However, egg-based production has some important disadvantages – it's slow, wasteful, and carries a risk of "egg adaptation" (see sidebar The Egg (and the Chicken) on page 33). In a bid to develop a faster, more efficient process, Chiron developed a vaccine grown in mammalian cells (dog kidney cells) in the early-2000s. The vaccine was launched in Europe, but it failed to find commercial success when pitted against well-established and inexpensive egg-based vaccines.

The emergence of H5N1 (bird flu) in the mid-2000s brought flu vaccine production into the spotlight. Concerned at the slow turnaround of traditional egg-based manufacturing methods, US government agencies showed renewed interest in cell-based alternatives. With government backing, Chiron (which by this time had been taken over and was, then, Novartis Vaccines) brought the technology from Europe to America, building a new factory in North Carolina – the same factory where we make our cell-based vaccines today. Novartis/Chiron also pioneered the use of an adjuvant called MA59 to boost immune responses to influenza vaccine.

The 2000s also saw the advent of the live attenuated flu virus, administered via a nasal spray (Flumist). Developed by Aviron (later Wyeth, then Medimmune and now AstraZeneca) this frozen vaccine, also produced in eggs, has had something of a chequered history. Initial trials showed it to be highly effective, but logistical challenges hampered uptake. Later, post-marketing data showed that it was not always as protective as hoped, leading to it being dropped from vaccination programs in some countries.

The next big innovation came in the 2010s from Sanofi – a recombinant protein vaccine (Flublok). Insect cells were genetically engineered to produce the most important surface antigen of the flu virus – hemagglutinin. The result is similar to cell culture-based production – faster manufacture and no risk of "egg adaptation."

Back in the early 2000s, everybody thought flu vaccination was a "dead" area with little hope of innovation. The changes we've seen over the past 20 years disprove that – showing that even long-established processes in pharma can be improved upon.

What are the most important lessons the industry has learned from manufacturing flu vaccines over the years?

Around 2005, my boss took a call from the head of CBER, the vaccine division of the FDA. They had just had to close down a major flu vaccine production facility due to quality concerns, which meant there was only one factory licensed to make the flu vaccine for the US market – a precarious position!

How did it come to this? The answer holds an important lesson – not just for flu vaccines, but for medicines more generally. In essence, flu vaccines had become so uneconomical to produce that manufacturers had pulled out. Those that remained struggled financially and started to slip behind in the quality standards demanded by regulatory agencies. When we, as a society, do not value important existing products and focus all our attention on new medicines, we leave ourselves vulnerable.

When H5N1 (bird flu) emerged in the mid-2000s, causing a number of infections in close contact and a mortality rate that suggested it had the potential to cause a pandemic to

MEET RUSSELL BASSER

I started off working at our parent company CSL almost 20 years ago. When the FDA requested that we bring our influenza vaccine from Australia to the US to combat vaccine shortages in the mid-2000s, my group led the clinical and regulatory project. The year 2009 saw the emergence of swine flu, and my group was responsible for supporting the Australian government in their response to the virus.

I found flu a fascinating area and later took on the role of head of R&D for the newly formed Seqirus – a semi-independent business under the CSL umbrella, focusing solely on flu vaccines. My role encompasses everything from basic research through to manufacturing development, clinical, regulatory, drug safety, and medical affairs.

rival Spanish Flu, the world was less prepared than it could have been. Fortunately, H5N1 has yet to develop the ability to transmit between people but remains a threatening presence in bird populations.

A less severe pandemic emerged in 2009 in the form of H1N1 swine flu, that swept across the globe, causing fatalities amongst children and pregnant women in particular. Since then, governments have been investing more heavily in flu preparedness, in the hopes of being ready for the next pandemic.

"There is a saying in the flu world that when you've seen one flu season, you've seen... one flu season. Every season is different."

What lessons about pandemic preparedness can we take from COVID-19?

We think of our seasonal flu vaccine campaigns as practice runs for a pandemic. We're very aware that companies like ours are an important line of defence for communities. COVID-19 is, naturally, the overwhelming focus right now, but new flu viruses remain a risk, and there are lessons we can take from COVID-19. One lesson is that days and weeks are very important, and ideally we should be prepared to take action quickly. In many countries, governments were initially slow to take decisive action; the delay has cost many lives.

Another lesson is how important it is to "know your enemy." SARS-CoV-2 is a new virus but is essentially similar to the viruses that cause SARS and MERS, for which vaccines were already in development before COVID-19 came along. That prior knowledge has enabled rapid development of vaccines for SARS-CoV-2; we already had a good idea of how the virus operates and had an existing target (the "S protein") that could be rapidly developed into a potential vaccine.

If a new flu virus threatens to take hold, I believe we are in a much better position to respond than we have been to COVID-19, with manufacturing and supply chains already in place around the world. Taking preparedness a step further, Seqirus has already registered a vaccine for H5N1 and gained regulatory approval in the US. If a pandemic were to emerge, we could start manufacturing a vaccine as soon as the genetic code of the strain responsible was sequenced. We believe we could have a vaccine available in as little as three months. We are already in talks with governments about developing similar "pre-pandemic" vaccines for other avian flu viruses, such as H7N9 and H5N6, in case they make the switch to human-human transmission. Over time, we hope to build up a portfolio of these vaccines, ready to roll out if we ever need them.

You can't be truly prepared until you have tackled something many times. Being prepared "on paper" is a bit like visualizing running fast or kicking a ball into a goal – it helps, but true expertise comes with action. I will remain somewhat cautious about new vaccine platforms until they are truly tested in the field.

Despite your caution, what developments in vaccines are you excited about?

Going back to pandemic preparedness, I believe some of the new technology platforms being developed in the vaccine space are another way in which we can become more responsive to new threats. For example, mRNA and vector-based vaccines could allow very rapid vaccine development. However, these

platforms have not been widely used to date and we need more information on safety and efficacy at a population level and over time to confidently rely on these approaches.

Vector-based vaccines, like the SARS-CoV-2 vaccine under development by AstraZeneca and the University of Oxford, are very interesting but, as the vector itself will generate an immune response, they may not be effective if administered more than once or twice.

mRNA vaccines, which get the body itself to produce viral proteins, also have amazing potential. We have an mRNA program at Seqirus and we've found that it is possible to generate a new vaccine in a matter of weeks. We've also seen very strong responses, even better than many currently commercialized technologies. However, there is much to learn about mRNA vaccines – they seem to cause quite marked reaction at the site of injection, as well as fever when administered at high doses. This latter property indicates that care will need to be taken when administering such a vaccine to young children, who can be especially sensitive to such an effect. Another challenge is that mRNA vaccines are very unstable and have to be frozen. This has been manageable during the development phase, but will add considerable complexity and cost in distribution to the general population, which will provide logistical problems

COVID-19 has brought these new platforms onto the fast-track with almost unlimited money and resources, which could have a positive impact on the field for years to come – and that's fantastic. But it's also important to remember that there is still a lot of work to do. As soon as a vaccine shows some success in clinical trials, the press and community at large has expectations that this will make the virus disappear and allow life to return to normal almost instantly. However, population vaccination programs will take time; the first generation of vaccines are unlikely to be perfect and we will continue to learn about their pros and cons along the way.

Is Seqirus involved in SARS-CoV-2 vaccine efforts?

We are partnering with the non-profit Coalition for Epidemic Preparedness Innovations (CEPI) and The University of Queensland (UQ) to help develop their protein subunit vaccine. They are using their molecular clamp platform, designed specifically for rapid response vaccine development. We have provided the MF59 adjuvant, an important additional element that stimulates the body's immune response to the S protein. The UQ vaccine is currently undergoing phase I trials, and we'll take responsibility for further development after this study is finished (and assuming it is safe and immunogenic). We have also been contracted to produce the AstraZeneca vector-based vaccine for the Australian Government.

THE EGG (AND THE CHICKEN)

Most flu vaccines are produced in the yolks of fertilized hen's eggs. It's a well-established, inexpensive method, but is it still fit for purpose in the 21st Century?

To produce flu vaccines, the WHO has a highly sophisticated surveillance program, with many different labs from around the world submitting samples of flu virus from patients in their area. Based on this information, the WHO makes a twice-yearly recommendation on which strains to include in the vaccine for the forthcoming flu season – once for the northern hemisphere and once for the southern hemisphere.

The chosen strains are then grown in just a few labs worldwide – including Seqirus in Australia, NIBSC in the UK, and the NIH in America. Eggs are not the natural habitat for the flu virus; it must adapt and mutate slightly to grow successfully in this alien environment. For egg-based production, the labs mix the chosen flu strains with a virus that's known to grow well in eggs and select the mutated virus that represents the best compromise between similarity to the "wild" virus and the ability to grow in eggs. These final strains are then distributed to the flu vaccine manufacturers to produce the flu vaccine for that year.

There is growing evidence that, in certain flu strains, the mutations that allow the virus to grow in eggs can affect the hemagglutinin proteins critical for the efficacy of the vaccine.

Hemagglutinin is the protein responsible for binding to and entering host cells – but the cells in the egg are not the same as human cells, so the protein must alter slightly to be able to reproduce in eggs: "egg adaptation." And so, when the immune system encounters the wild-type protein, it only partially recognizes it. In years when the dominant flu strain is affected by egg adaptation, egg-based vaccines may be significantly less effective. There are also other challenges associated with egg-based vaccine manufacture. Production is slow (six months), relies on a massive supply of eggs (up to three eggs per dose), and it generates a lot of waste.

Alternatives are available – a vaccine grown in mammalian cells (from Seqirus) and a recombinant vaccine (from Sanofi Pasteur). There is evidence that these egg-free vaccines offer enhanced protection (1), with larger studies underway (2). They are also faster than egg-based methods, offering the hope of a rapid response to any new pandemic strain.

Other companies are looking into a variety of approaches, from growing virus-like particles in plants to mRNA vaccines that cause the body's own cells to produce flu proteins (3).

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Credit: Navy Medicine from Washington, DC, USA

But your main focus remains flu?

That's right. Seqirus has been an extraordinarily successful industrial experiment! We took unprofitable parts of two companies and created a successful entity, focusing solely on the then-unfashionable area of flu vaccines. The secret of our success has been to keep that focus narrow and deep on the single disease area. Flu is more difficult than most other vaccines, so our laser focus is essential.

There is a saying in the flu world that when you've seen one flu season, you've seen… one flu season. Every season is different. This is one aspect that distinguishes flu from all other vaccine fields – we're constantly chasing a mutating virus, but never quite catching up to it. Even with all the advances in medicine, flu remains a challenge. Sometimes the vaccine is very effective, and sometimes the virus drifts after the vaccine strains are chosen and efficacy drops off dramatically.

The deep expertise we've developed in flu has allowed us to innovate; in particular, developing the MF59 adjuvant and the cell culture platform I mentioned earlier. Now, we're combining the two advances. We've already done this for our pre-pandemic vaccines, and we hope to soon apply the same combination to create the very best annual vaccine possible with current technology. It's an exciting direction!

Do you think we'll ever see a universal flu vaccine?

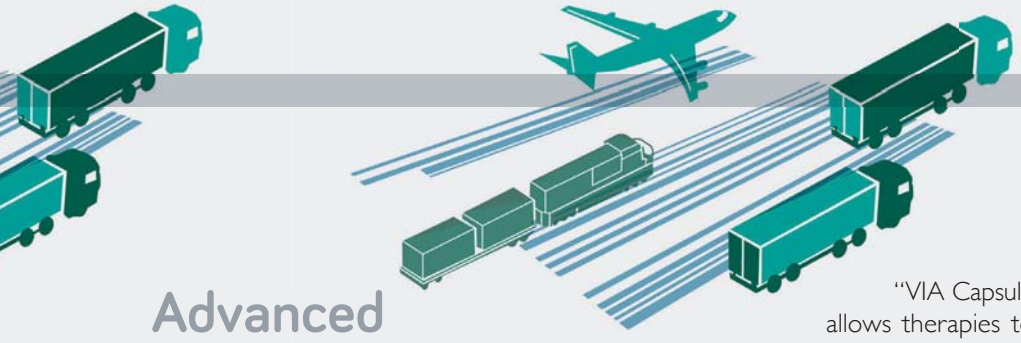
The press was very hot on this around five years ago and I still get asked about the potential. It is certainly a wonderful prospect: a single vaccine that confers lifelong immunity to all strains of flu. But, as one of my mentors told me, the less you know about something, the more exciting it is. Knowing what I do about the flu virus, I doubt we'll see a universal vaccine within my working life.

It's easy to believe fantastic advances like the recombinant HPV vaccines – which require only one dose to provide lifelong immunity – are possible for all viruses. But flu is a different proposition as there are four separate viruses, all mutating rapidly. Before we can even begin to think about a universal vaccine, we need to know a lot more about how the virus behaves in the body and find strategies to trick the immune system into generating a stronger and more long-lived response.

To that end, we participate in a public–private partnership group, the Human Vaccine Project, which is mapping the intricacies of the human immune system down to individual molecules. The aim is to better understand how the body responds to infection and vaccination to see if we can uncover some secrets that might help us generate better vaccines. The exploration is fascinating, exciting and extremely complicated – the more we know, the more we realize we don't know!

For me, flu is one of the most fascinating spaces to be in. It combines immunology, virology, public health, and geopolitics. And that means it is constantly changing – and constantly challenging.

Russell Basser is Senior Vice President, Research & Development at Seqirus, Australia



Advanced Therapies – VIA Capsule™ System

Confidently ship and monitor precious samples without liquid nitrogen

Cell and gene therapies have the potential to change lives and even cure diseases. It is critical that these products maintain their quality during transport, even when there are delays. With all of this in mind, cryobiologists at Cytiva developed a liquid nitrogen-free system to ship cryopreserved products in a controlled and confident way. Liquid nitrogen requires specialized handling – and many of the facilities that will ultimately treat patients with advanced therapies are not set up for this.

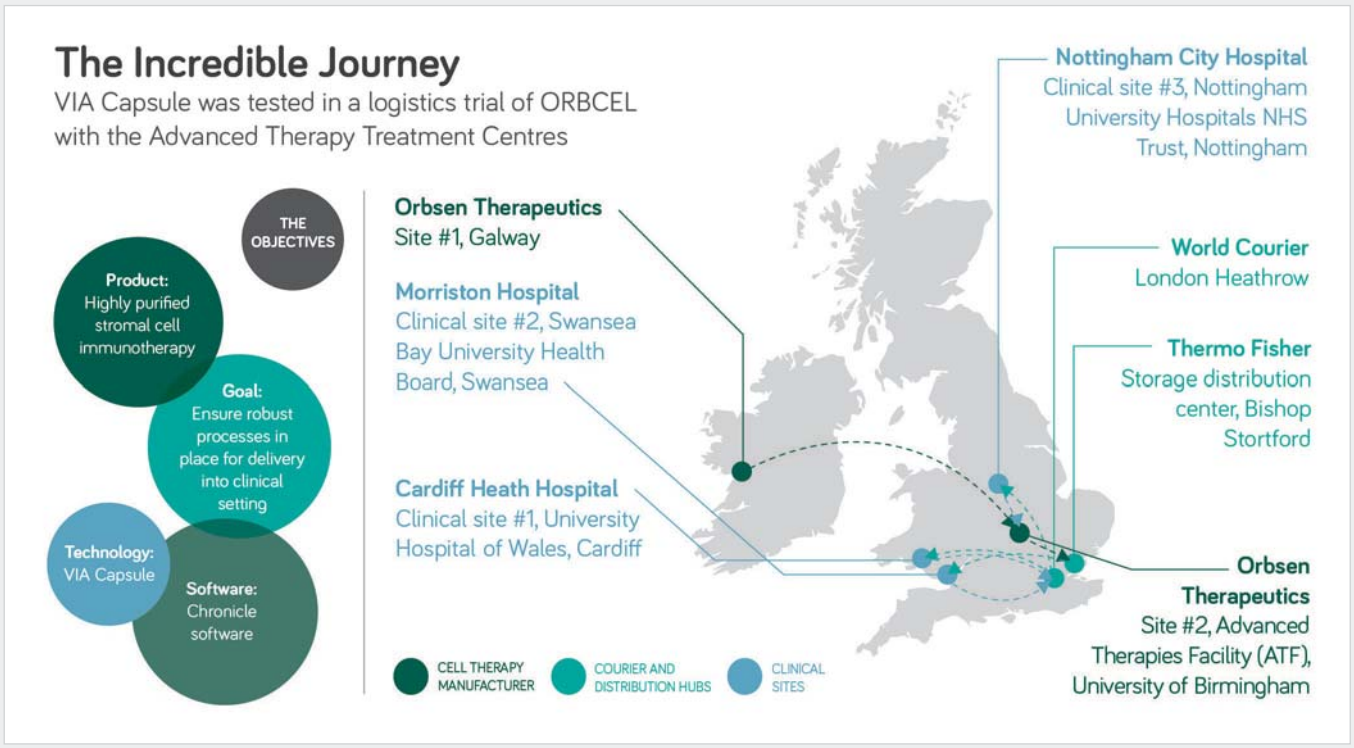
"VIA Capsule allows therapies to be delivered safely and securely without liquid nitrogen, avoiding the associated complexity, risks, and inefficiencies," says Bill Shingleton, Alliances Manager at Cytiva. "It can be used for shipping cellular products from manufacturing centers to clinics, and also for shipping cell therapy starting material."

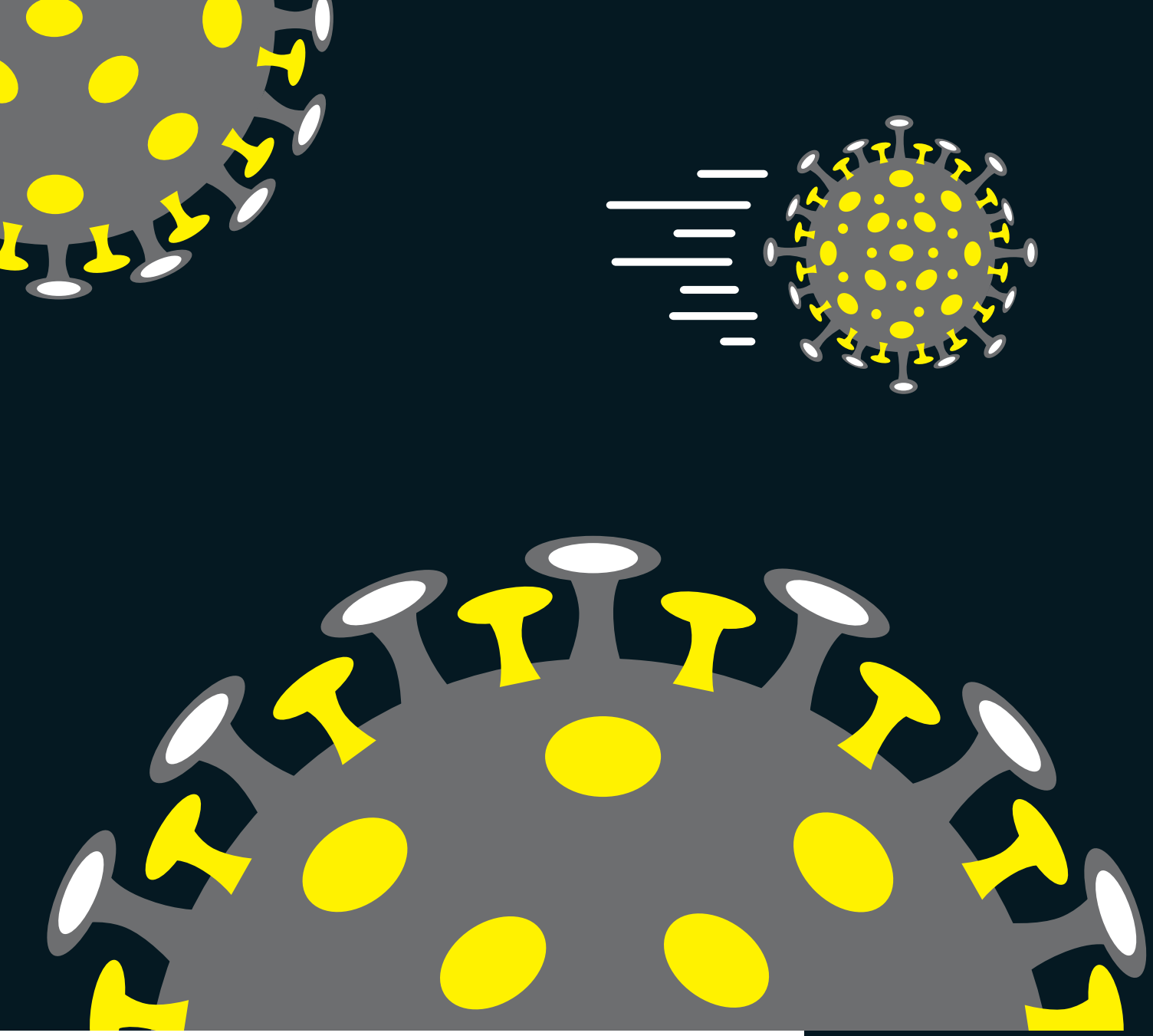
A major benefit of the VIA Capsule system is that it tracks where the product is at any time. It also monitors the temperature and the angle of the system throughout the journey, providing real-time alerts if thresholds are exceeded. "The status can be monitored using Chronicle™ web-based software, which can be accessed from different devices, including tablets and phones. Clinical staff at the receiving sites can also have oversight of when the drug will arrive so that they can prepare patients accordingly," says Shingleton.

During testing the VIA Capsule system traveled far and wide – over 80,000 km across Europe, Asia, and North America. A key partner for the VIA Capsule logistics process is World Courier, which has hubs across the globe. World Courier performed its own testing and validation of VIA Capsule to ensure that it meets the quality they seek in shipping systems.

The graphic below shows how VIA Capsule was used in a UK logistics trial with the Advanced Therapy Treatment Centres (ATTC network) and Orbsen Therapeutics to transport a stromal cell immunotherapy, ORBCEL™. The result? Viability of cells shipped using VIA Capsule was similar to the viability of cells retained at the original site.

Find out more in the webinar available at: https://themedicinemaker.com/webinar/advanced-logistics-for-advanced-therapies-evidence-using-via-capsuletm-cryogenic-system





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From Big Pharma to New Green Horizons: Lessons Learned with Ross Burn

With just a three-day crash course in business finance under his belt, analytical chemist Ross Burn co-founded CatSci in 2010. Here, he talks about surviving and thriving as a new company focused on process chemistry, alongside more recent moves into industry 4.0 and collaborations in the contract research space.

Let your profession choose you

Having an interest in chemistry and being someone who enjoys solving problems meant that analytical chemistry was a great fit for my MSc. That's what I studied at Strathclyde University – along with forensics. This was back in 1998-2003 before forensic chemistry hit the mainstream with CSI! Even then, some people had this idea that they'd be helping to solve crimes or giving evidence as an expert witness in court, but the day-to-day job of a forensic scientist tends to be quite routine.

I was always more inclined towards the analytical side – I especially enjoyed separation science and investigative analysis. And that led me to study for a PhD, funded by Pfizer, based on analyzing the human proteome and trying to find new biomarkers of disease. There, I was exposed to the workings of drug development within a large pharmaceutical company and began to appreciate the role analytical science plays in bettering human health. So, while I couldn't see myself going down the forensic side, you could say pharma chose me!

A big pharma company allows you to develop into a top-class scientist

After my PhD, I was fortunate to get my first role at AstraZeneca. After having spent several years at Pfizer during my PhD and then at AstraZeneca as a process chemist, I realized that large pharmaceutical companies know how to develop top class scientists. Not only are you working with cutting edge equipment, but you're learning from experienced professionals who are brilliant at following the science towards answers to complex practical problems. Big pharma gets a lot of bad press, but my experience was that they empowered us to be the best scientists we could be. You can see why many are happy to spend their entire careers within a large pharma company, but that wasn't my path…

You need thick skin to build new relationships from scratch

In 2010, AstraZeneca decided to reduce its R&D footprint and shut down several sites in the UK. But they wanted to retain what we were doing well in the Bristol lab: catalysis screening. So, four colleagues and I decided to set up an independent lab and service AstraZeneca's portfolio until they were able to recreate the facility in Macclesfield.

Although for a period of time we were carrying on the work we were doing as AstraZeneca employees, I noticed some significant changes when trying to find new contracts. Without a big pharma name, building new relationships from scratch wasn't easy and we had to grow thick skin to handle rejection. I also took on the financial responsibilities of the company from the start, in addition to working on the science, business development, and leadership. Finding the right work/life balance was tough while we honed our entrepreneurial skills and fought to create a sustainable business.

Fortunately, the UK government at that time ran a three-day crash course in business skills that taught you the essentials as a business owner. And AstraZeneca were kind enough to allow us to take some time during our final months to educate ourselves. They did that for anyone looking to change careers as part of their winding down process.

A 40-second elevator pitch is worth more than a 100-page business plan

I realized early the importance of having a good value proposition – and that's what really got us going. My advice to anyone looking to set up a business is, don't expect it to be something like Dragon's Den! Ensure you thoroughly carry out your market research, validate that your product provides a value-add or a solution to a current problem or need, and make sure your product or service is market ready at launch. There are startup networks and accelerators available that function as sounding boards for testing your hypotheses and prepare yourself for many years of hard graft to build a sustainable business.

And as a new business you will need funding – cash is king, as they say. Traversing the entrepreneurial valley of death from startup to breakeven isn't easy.

"Without a big pharma name, building new relationships from scratch wasn't easy; we had to grow thick skin."

We're a bootstrap business, which means that we are owned by the co-founders and we don't have any capital partners that inject cash into our business. The upshot is that we started the business with bucket loads of sweat equity, and still to this day reinvest as much of our profits as possible to fuel our business to grow. We also take on significant risk accelerating growth by leveraging additional bank debts into the business.

We decided to focus on sales and marketing from the beginning and assemble the best team we could. The goal was to get beyond the breakeven point as quickly as possible and to plan our funding needs from there. There are a number of great schemes available in most countries (in the UK, one can take advantage of the Entrepreneur Investment Scheme) that allow companies to raise external finance quickly. Remember, there's trillions of dollars in the ecosystem waiting to help a business start and scale up – you just need the right business and team to make it happen.

I wouldn't recommend spending weeks writing a 100-page business plan in the early stages. Instead, make sure to refine your sales and marketing strategy so that you can clearly explain your value proposition – one that will resonate with stakeholders – in 10 slides or so. Having a

40-second elevator pitch to grab people's attention is vital.

Don't be afraid to re-evaluate when things don't go to plan

We were lucky enough to have our first client, AstraZeneca, in the bag at launch and we managed to win business quite quickly. But that turned out to be a false dawn. Many of our initial customers were intrigued to see how we were using AstraZeneca's honed methodology, which we owned, to solve catalysis problems. They wanted to see what sorts of processes AstraZeneca was using and perhaps didn't intend on giving us repeat business.

In the end, we decided to shift our business model from catalysis screening to pharmaceutical process research and development. Many of our initial projects were in other sectors such as chemicals and agro. We decided to use catalysis as a tool to solve problems in the pharma industry and go back to what we were always good at: developing chemical processes for small molecule medicines. Since we made the change, we've grown an average 50 percent year-on-year.

Consider the environmental impact early or risk trouble down the road

Another key decision we made was to focus on green chemistry. I believe we should do our best, as a company and an industry, to reduce our carbon footprint and minimize the use of finite materials. Many processes use platinum group metals that predominantly come from just two countries: South Africa and Russia. Our approach is to use iron or base metal catalysis, which are far more abundant. The environmental case is clear but there's also an economic argument. Such rare materials will continue to increase in price and you are limited in terms of building redundancy into your supply chains – something people are increasingly concerned about due to COVID-19, Brexit and global trade negotiations.

We passionately believe that companies need to be thinking about the environmental impact of their processes early. We see a lot of emerging companies developing new chemical entities. Often, they aren't looking to commercialize the process themselves so environmental concerns aren't near the top of their priorities. But companies must be aware that, even if you're making kilos of API, the process mass intensity could be huge – especially if you have a high number of steps. We try to explain that companies need to be thinking about the process at the candidate selection stage because you don't want an inefficient process with considerable environmental impact down the road.

Fortunately, the industry as a whole is becoming more environmentally conscious. The big pharma companies all have green metrics to which they try to aspire – in turn, that's putting pressure on CMOs and CDMOs, as well as the smaller companies, to follow suit. Over the next 5–10 years,

I believe most companies will have good green metrics in their objectives.

Never underestimate the importance of staff wellbeing

Of course, we, along with everyone else, are having to adapt to the new challenges associated with COVID-19. We were allocated key worker status and were open throughout lockdown and we never had any confirmed cases of COVID-19 within the company. We couldn't operate quite as effectively as usual but we managed to deliver on the projects we had booked. Like everyone else, we had to accelerate our digital strategy by probably 5 years, with managers and leaders working from home and interacting digitally with their colleagues. But we were already quite familiar with tools like Teams and Zoom because we have an international sales team.

The impact on the business wasn't as severe as other industries and companies. The real challenge for us was the wellbeing of staff. People react differently to an existential threat like a pandemic and many were anxious. Finding ways of making sure that everyone felt supported – with so much negativity in the press and people worried about their loved ones – was tough when working remotely.

In terms of our clients, they fell into two camps. In camp one, they knew how to proceed. They had their own milestones to hit and they decided to proceed as normal. In camp two, companies were more inclined to hold off on making decisions on repeat business until they had a better idea of when lockdown was going to end. This delayed decision making did give us some concern, but now we're back to business as usual.

Digital technologies are coming, but collaboration is also key to innovation

When we talk about the (digital) future, we're talking about CatSci 4.0. Phase 1 was the initial founding, phase 2 was the switch to process research and development, and phase 3 involved bringing in a new senior management team. Now we're planning on further embracing industry 4.0 concepts: using in-silico tools for chemistry, using bots for automated back end processes in the business, intelligent automation for parallel synthesis, and integrating artificial intelligence across the business. The idea is to free up the minds of the chemists to solve the difficult problems.

We're also seeing a trend away from the traditional contract research organization towards "innovation partners." Much of the innovation in the industry is coming from the smaller, emerging pharma companies and the supplier "CROs", with pharma companies outsourcing more and more – potentially to the extent that a candidate may be outsourced all the way through to the clinic. But many companies are thinking too bilaterally with their collaborations. For example, they might have an outsourcing manager that has conversations with parts of the value chain, but the niche CROs and CDMOs never work together. We believe we can disrupt that thinking and work more collaboratively. We're now forming partnerships with other niche organizations in the UK and overseas to bring new innovation to the industry. In fact, we recently announced new partnerships with three UK companies across the pharmaceutical supply chain – M2M Pharmaceuticals, New Path Molecular and Upperton Pharma Solutions. This collaboration will ensure that customers can access specialised capabilities and expertise throughout the journey from molecule to medicine.

Ross T. Burn is CEO at CatSci Ltd

Fighting Viruses with Enhanced ADCC

With evidence mounting for the importance of antibody-dependent cellular cytotoxicity in controlling viral infections, mAbs engineered to enhance the effect are primed for success

Andrew J. Racher PhD, R&D Director – IP Strategy at Lonza

Antibodies form an important feature of the host adaptive immune response to viral pathogens. Passive administration of antibodies obtained from convalescent patient plasma is a well-established concept (1), for example, as part of the treatment regimen following exposure to rabies virus. Building upon this concept, a number of recombinant mAbs have been developed over the last 25 years for treating viral infections (2). At the time of writing, there are six antibody therapeutics approved for the treatment of viral infections. Two of these antiviral antibody therapies are cocktails of at least two mAbs. As of early November 2020, there are sixteen mAbs in clinical trials for the treatment of COVID-19 that target the SARS-CoV-2 S protein (3). Three of these mAbs are Fc-modified to reduce the likelihood of antibody-dependent enhancement of virus infection, to extend half-life, or to enhance binding to immune-activating receptors.

Researchers are always looking for new ways to improve effectiveness of antibody therapy – often by engineering cells to enhance certain immune mechanisms. One such promising mechanism is antibody-dependent cellular cytotoxicity (ADCC).

Following the initial virus challenge, there are a number of processes – such as neutralization and agglutination – by which antibodies directly prevent viral infection. Binding of a virus-antibody complex to an Fc receptor on a phagocyte can trigger phagocytosis, resulting in destruction of the virus (see Figure 1). Binding to the Fc receptors on immune effector cells, such as monocytes, neutrophils, eosinophils and NK cells, trigger the release of cytotoxic factors (for example, antiviral interferons), creating a microenvironment that is hostile to virus replication. Various research groups (4–8) have demonstrated that broadly-specific neutralizing mAbs targeting highly conserved regions of haemagglutinin (a glycoprotein found on the surface of influenza viruses and integral to their infectivity) require Fc-mediated effector functions, especially ADCC, to protect against influenza virus challenge in vivo. Therefore, enhancing the potency of ADCC could be an effective way of combating influenza virus infection.

ADCC may be important in controlling other viral infections too. For example, researchers have successfully treated HIV-1 with broadly-specific mAbs in animal models (9–11). They attributed this success to both the neutralization function of the anti-HIV-1 mAbs, as well as their ability to activate ADCC – which removes infected cells. ADCC is also considered a potentially important mechanism for protective immunity in herpes simplex virus infections (12). It has also been shown that serum antibodies against hepatitis C virus E2 protein can mediate ADCC (13,14). Taken as a whole, there is growing evidence that ADCC is a significant component of the adaptive immune response to virus infection, highlighting the importance of strategies that induce and enhance ADCC in vaccine development.

Enhancing ADCC

How might researchers go about enhancing ADCC? The principal receptor for NK cell-mediated ADCC is the low affinity Fc gamma receptor, FcγRIIIa (CD16a). FcγRs bind to a region in the hinge and proximal CH2 region within the Fc fragment of antibodies, with IgG1 and IgG3 interacting most efficiently. This interaction is critically dependent on the glycan at the N297 site in the CH2 region (15). Removal of the entire N-glycan structure reduces the binding of Fc to FcγRs, and reduces or eliminates the associated effector functions. Conversely, eliminating only the fucose residue from the core glycan structure creates an afucosyl mAb and strengthens the binding of a mAb to FcγRIIIa receptors, enhancing ADCC (16–18). The strength of Fc-FcγR interactions can also be modulated by mutating the Fc region (19).

This mechanism also has support from Desheng Kong and colleagues, who showed that an anti-HIV-1 afucosyl-bispecific antibody had a greater ability to kill HIV-1 infected cells through ADCC than the fucosylated form (20). Another study found that enhanced ADCC was a potential mechanism for protection against Ebola virus infection, with afucosylated mAbs having up-to an approximately 11-fold lower ED50 than fucosylated mAbs (21).

The growing evidence for the importance of ADCC in controlling viral infections suggests that mAbs engineered to enhance ADCC (for example, through production in CHO FUT8 knockout variants of the host cell line (such as Lonza's POTELLIGENT® CHOK1SV®) will become an important element of successfully treating viral infections. Recent studies (22,23) point towards the potential importance of strategies that target effector function pathways. Schäfer and colleagues (22) report that intact Fc effector function is required for protection from SARS-CoV-2 infection. Chakraborty and colleagues (23) report lower Fc fucosylation in antibodies to the receptor binding domain of the SARS-CoV-2 spike protein in adults with PCR-diagnosed COVID-19 compared to SARS-CoV-2-seropositive children and relative to adults with symptomatic influenza virus infections. This suggests strategies

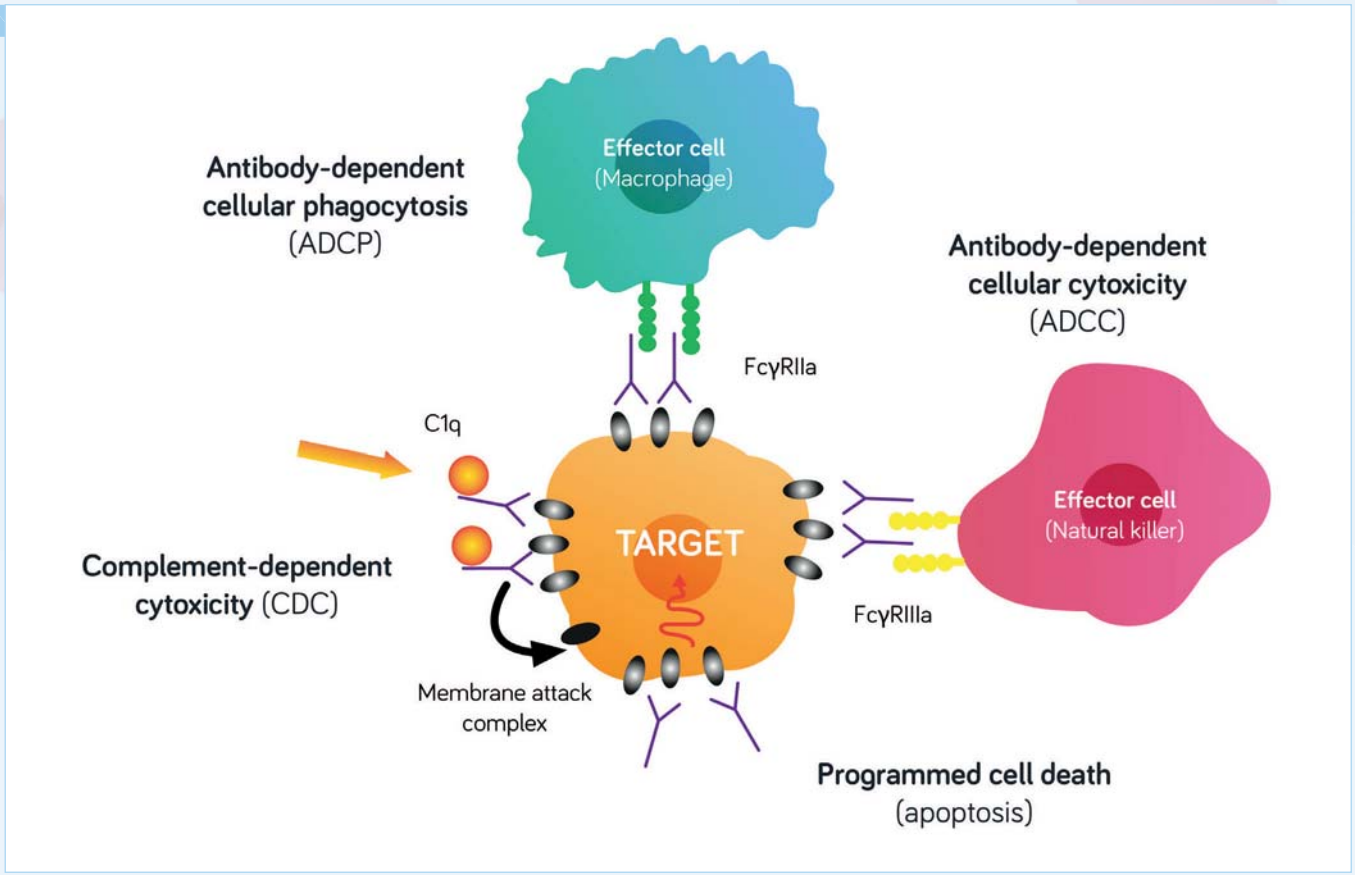

Figure 1. Antibody modes of action. Cell lysis through activation of complement dependent cytotoxicity (CDC); interaction with Fc receptors on effector cells to engage antibody dependent cellular cytotoxicity (ADCC); signaling for ingestion of a pathogen or target cell by a phagocyte.

that target FcγRIIIa pathways may have therapeutic benefits. The enhanced ADCC activity of reduced fucose antibodies could contribute to viral clearance through killing and removal of infected cells. As overactive ADCC function may exacerbate symptoms in some cases, it will be important to carefully dose mAbs with high levels of effector function. Recombinant low fucose or afucosyl mAbs produced using CHO cells would form an important element of a strategy to produce mAbs with high-level ADCC effector function.

The adaptive immune response to virus infection is complex, involving the production of a broad repertoire of antibodies that interact with a range of Fc- and other receptors. As such, potent Fc-engineered or glycan-engineered mAbs with enhanced ADCC activity may form part of an antibody cocktail that mimics the nuanced in vivo response to virus infection – and a number of mAb-therapies for treating virus infection are already cocktails of at least two mAbs. Such antibody cocktails simultaneously target non-overlapping epitopes minimizing the likelihood that the virus becomes resistant to treatment.

The field has come a long way since the approval of the first therapeutic mAb in the 1980s. Today, we may be witnessing, as Alicia Chenoweth and colleagues (24) have alluded to, the "next-gen" of antibody therapies, with researchers taking new findings from immunology and using them to tweak and improve existing treatments. These next-gen biologics may unlock the full potential of antibody immune therapies – bringing new and exciting treatments to patients with difficult- or impossible-to-treat diseases.

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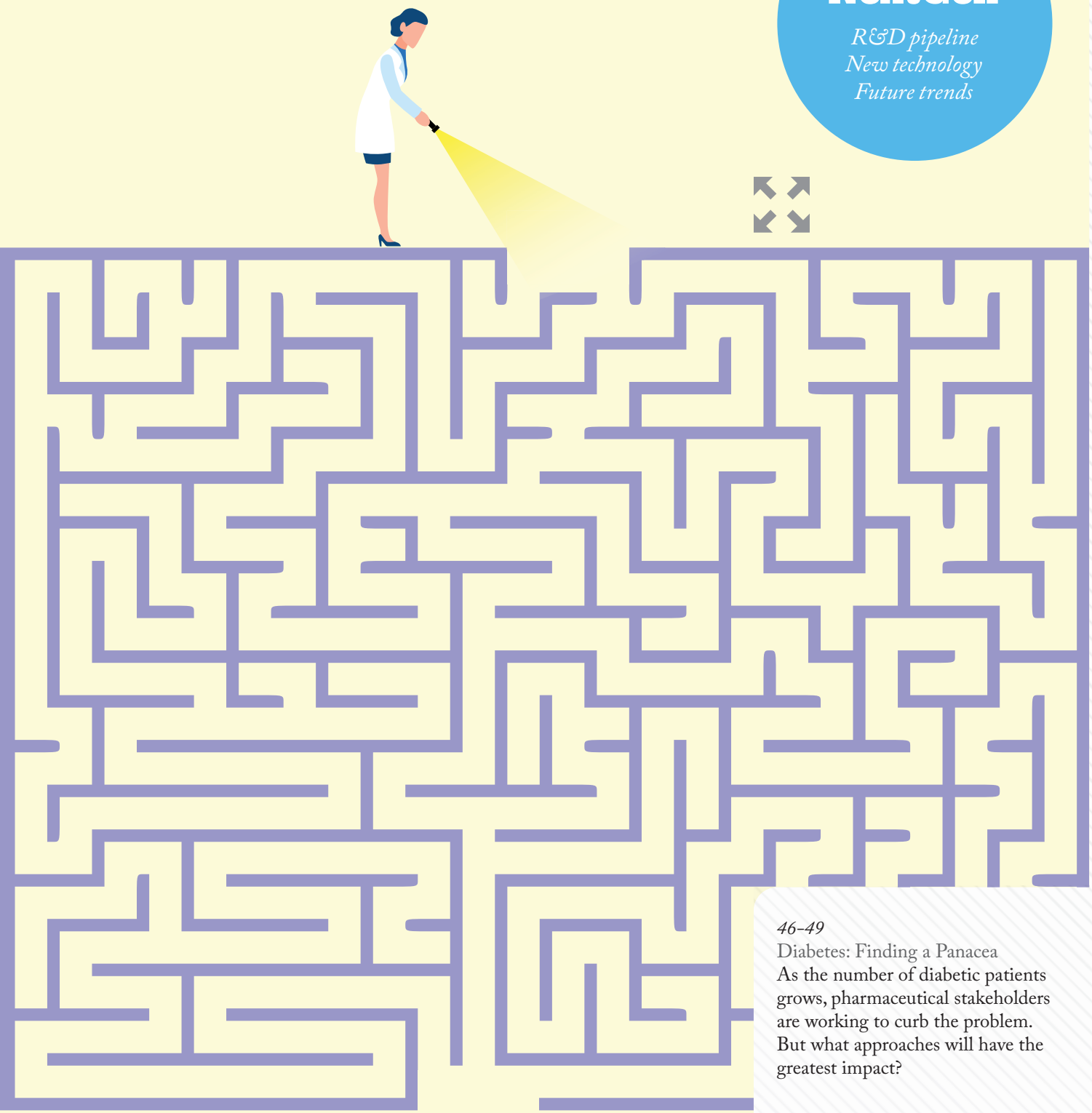

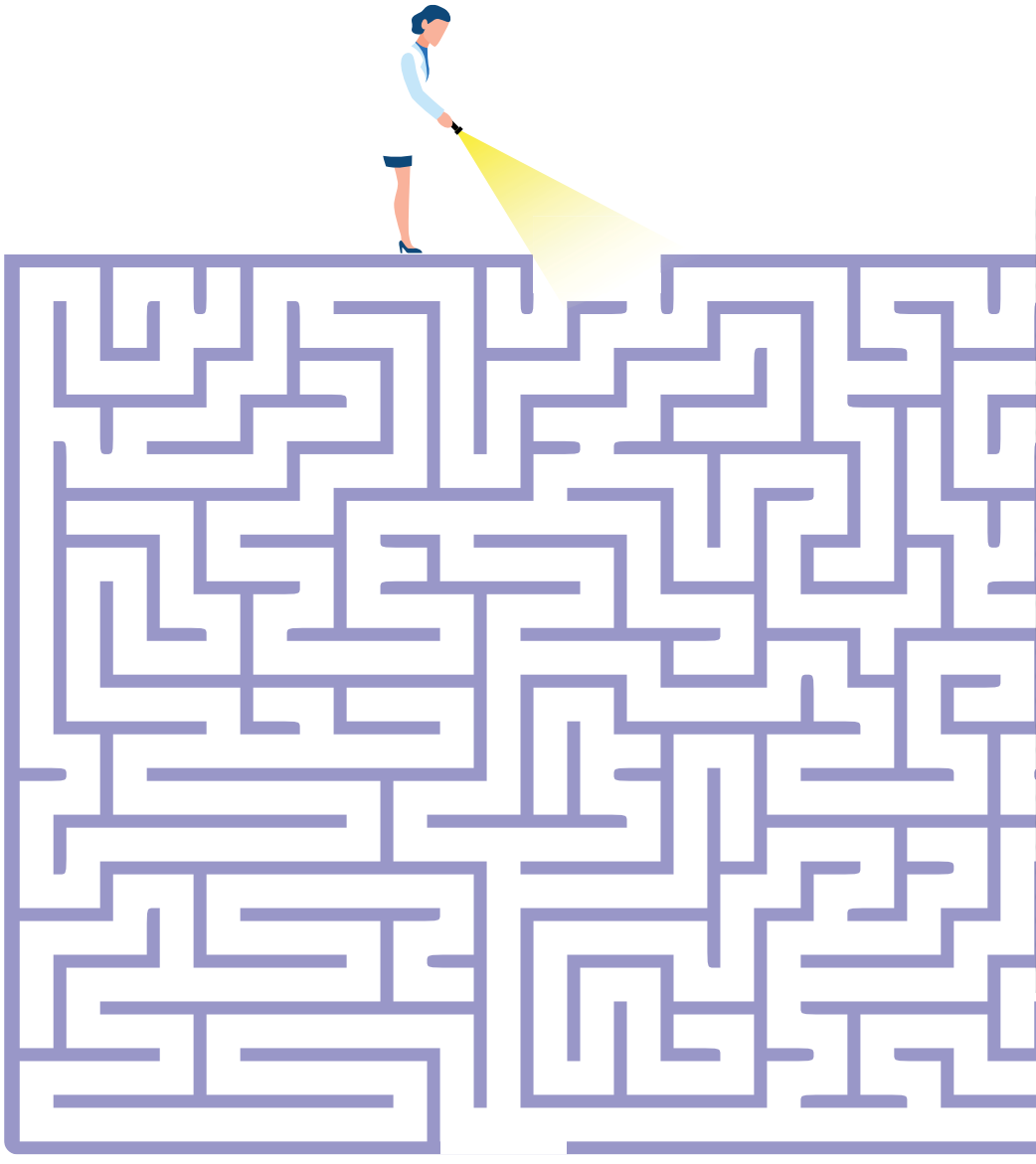

Diabetes: Finding a Panacea

What is pharma doing to reduce the global incidence of diabetes?

By Maryam Mahdi

In 2013, world leaders came together to develop an action plan to address the global rise in noncommunicable diseases (1). Among the goals was to prevent further increases in the number of cases of diabetes mellitus (types 1 and 2). But adequately addressing the current epidemiological situation is a challenge; over 400 million people worldwide live with diabetes (5-10 percent of individuals live with type 1) and estimates suggest that the number will continue to rise (2,3). The high disease burden has placed significant stress on countries' economic and healthcare infrastructure.

According to Kiran Mazumdar-Shaw, Founder and Executive Chairperson of Biocon, ensuring proper disease management is crucial to curbing this global healthcare problem. "Diabetes is often described as a disease of halves – only half of the people living with it get diagnosed; only half this group receive treatment; and, among this group, only half are compliant with their medication," she says. "Although early insulinization is regarded as an efficient aid to improve long-term control and the quality of patient lives, this method of treatment fails to address certain problems." Needle anxiety and issues related to cold chain supply, particularly in rural areas of developing countries, may delay the onset of treatment, she adds – problems exacerbated by the stunted growth of the treatment pipeline.

"Insulin has been used as a life-saving treatment for close to 100 years," says Stephan Kissler, Associate Professor of Medicine at Harvard Medical School. "Though the types of insulin preparations available have continuously improved, as have methods of administering them – with smaller needles, insulin pens, and automated pumps available today – we still don't have a treatment to prevent or cure diabetes."

This leaves the door for innovation wide open. But before new options can be developed, Mazumdar-Shaw believes that the pharmaceutical industry can do more to improve access to existing treatments.

"Addressing the current epidemiological situation is a challenge; over 400 million people worldwide live with diabetes."

The price of good health

In recent years, debates about the price of insulin have swirled around industry spheres. Though a necessary treatment for all type 1 and some type 2 diabetic patients, the cost of the drug has continued to rise. In the US, for example, a single vial of insulin can cost US$250, preventing the most vulnerable from accessing it (8). "The lack of equitable access to affordable insulin remains a key impediment to successful treatment and results in comorbid complications and premature deaths," Mazumdar-Shaw says. "Not only are people with diabetes in low- and middle-income countries struggling to manage their condition, but even those in developed markets are forced to ration insulin due to its high cost. It is an untenable situation because, despite being universally available for nearly a century, insulin is yet to be universally accessible."

Insulin-dependent diabetes patients have to contend with a large price differential between recombinant human (rh-) insulin formulations that tend to be more affordable and pricier insulin analog formulations. Insulin analogs are genetically engineered to produce either long-acting or rapid-acting forms of the drug. They differ from rh-insulin in that more changes are made to their amino acids to allow for their faster or prolonged action in the body.

"The increasing use of insulin analogs compared with rh-insulin in the recent past – especially in the developed world – has meant that many are forced to choose between going into debt or cutting back on medication," she continues. So, with these difficult decisions to make, what can the industry do to better support patients?

For Biocon, the answer lies in creating solutions for emerging and developing markets. "Using our proprietary platform technology that relies on Pichia pastoris – a yeast species – we can manufacture cost-effective rh-insulin and insulin analogs," says Mazumdar-Shaw. This proprietary technology offers an efficient and optimized process for manufacturing insulin.

And though companies are proving that they are committed to positively impacting patient lives, there is still more that can be done to ensure therapies are affordable and accessible. Time will be the determining factor in seeing real change.

The immunotherapy approach

According to Kissler, researchers have spent decades trying to understand type 1 diabetes and devise effective therapies. "In recent years, the field has recognized that, instead of solely targeting the immune system that causes the destruction of insulin-producing cells, an alternative approach might be to protect these cells from the immune system instead. This is a relatively new strategy that holds much promise," he says.

For Lucy Walker, Professor of Immune Regulation at University College London, immunotherapy may hold the key to tackling type 1 diabetes. Leading a team of researchers, she has begun to investigate how existing immunosuppressive therapies can be applied to the disease. "Immunotherapy has completely changed the landscape of cancer care and I am really excited to see it starting to come to the fore in autoimmunity," she says. "There are, understandably, more barriers to testing new therapies in people with type 1 diabetes, who are often young and otherwise healthy, than in people with advanced cancer. However, recent studies show that T cell-directed immunotherapy could delay the development of the condition by two years." Last year, the EMA awarded Priority Medicines designation to teplizumab – a drug that binds to the proinflammatory T cell co-receptor CD3, preventing it from killing insulin-producing cells. It also received a breakthrough designation from the FDA. The drug was shown to slow the onset of type 1 diabetes in at-risk patients by two to three years (4). The potential of this therapy, coupled with other recent results, has been a source of inspiration for Walker, whose work on abatacept – an immunosuppressive drug – could help treat the condition. In 2014, she found that T follicular helper cells were partly responsible for the destruction of the pancreatic beta cells that produce insulin. Now, in a project funded by Diabetes UK and AstraZeneca, Walker is exploring the role of abatacept in reducing T follicular helper cell numbers and thereby protecting insulin-producing cells. So far, the drug – currently used to treat rheumatoid arthritis – has been shown to help some people with type 1 diabetes, but not others, but the study must be expanded for its full potential to be realized.

Walker's work is just one example of the innovative research taking place to help people living with diabetes; many

It's Complicated

Addressing the cardiovascular risks associated with type 2 diabetes

Though many diabetes patients comply with treatment, others struggle – and, left unchecked, the disease can lead to several comorbid conditions. Stephen Gough, Chief Medical Officer at Novo Nordisk, discusses the impact of one such complication – cardiovascular disease – on type 2 diabetic patients and how the pharma industry is trying to help.

How has the treatment of diabetes evolved?

The pharmaceutical industry has come a long way in its ability to address diabetes. At Novo Nordisk, for example, we developed our first insulin products in 1923 and continue to produce treatments for both type 1 and type 2 diabetes today. Metformin, DPP-4, SGLT-2 inhibitors, and recent innovations like GLP-1 RAs are especially effective in blood glucose-lowering in comparison to previous treatments, but there are still issues for pharma to address. For example, we need to innovate on the drug delivery front. Injectable therapies, though useful, aren't suitable for everyone. Exploring new options will help us better support patients.

What challenges do patients face?

Diabetes is associated with many other conditions – including cardiovascular disease, the leading cause of death and disability in type 2 diabetes patients. We recently conducted a study, CAPTURE, to address a gap in the knowledge of the global prevalence of cardiovascular disease, as well as its risk and management in people with type 2 diabetes (1). Nearly 10,000 participants took part in the global study. We found that one in three people with type 2 diabetes have established cardiovascular disease (CVD), and 90 percent of those had atherosclerotic CVD (a build-up of fat, cholesterol, and other substances in the artery walls). The study also showed that only 20 percent of people with type 2 diabetes and atherosclerotic CVD are receiving a glucose-lowering treatment with proven cardiovascular benefits.

These data show that people with type 2 diabetes need to be more aware of their risk factors, and that physicians need to not only actively screen for them, but also prescribe blood glucose-lowering therapies with proven cardiovascular benefit if patient outcomes are to be improved.

What are you doing to help?

We developed an oral form of semaglutide – a GLP-1 RA – that works by boosting insulin levels and stabilizing blood sugars. Previously, the GLP-1 Ras were only available as injectables and, despite the efficacy in reducing hyperglycemia, body weight, and cardiovascular risk, only 5-10 percent of people with type 2 diabetes are treated with a GLP-1 RAs.

Our oral formulation was approved by the FDA in 2019, but our GLP-1 RA portfolio isn't limited to this one option. Injectables are still a vital part of the diabetes management landscape, so we also manufacture a once-weekly injection of semaglutide, which also helps combat the symptoms of type 2 diabetes. We're also working on a once-weekly insulin injection, icodec. It's important to expand the variety of available treatments to suit the broad and varied needs of people with diabetes.

What steps need to be taken for the future of diabetes management?

Recent clinical guidelines from professional bodies, such as the American College of Cardiologists and the American Diabetes Association emphasize the importance of an integrated, multidisciplinary approach to treating diabetes – in particular, bringing together endocrinologists and cardiologists – to reduce the cardiovascular risks and other potential complications of this disease.

For us, partnerships with policymakers and with organizations in the public-private space is integral. Two examples of initiatives we're involved in are Changing Diabetes and Cities Changing Diabetes. Through the former, we work alongside patients, lawmakers, and healthcare professionals to address diabetes risk factors in urban areas, ensuring that people with diabetes are diagnosed earlier and that they have access to adequate care. Through the latter, we collaborate and form cross-sector links with businesses and organizations to build cities that help us all live healthier lives.

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others are working on new treatments. Researchers at Texas A&M University's College of Medicine, for example, have reported on an immunotherapy that was shown to reduce inflammation and halt immune attacks on beta cells (5).

The Type 1 Diabetes UK Immunotherapy Consortium is also conducting several trials to investigate the potential of immunotherapies. This includes the USTEKID Phase II trial, which is investigating whether ustekinumab – a drug first produced by Janssen to treat psoriasis – will be effective in preventing pancreatic damage (6).

Other research teams are approaching the problem by using currently available small molecules to their advantage. "Repurposing an old drug that is off-patent has the benefit of potentially making a very cheap drug available to patients," Kissler says. "Because a repurposed drug does not have to undergo lengthy preclinical development and the many stages of toxicity and safety testing, its cost can remain low."

Though scientists have developed methods of creating insulin-producing cells by resetting the pluripotency of blood and skin cells – allowing them to be converted into pancreatic beta cells – the risk of their destruction by the immune system still remains. With this in mind, Kissler and his colleague Peng Yi at the Joslin Diabetes Center are investigating how a drug first developed in the 1950s could prevent the autoimmune killing of beta cells.

Using a genetic screening approach, the researchers discovered an enzyme, renalase, that had previously been associated with the risk of type 1 diabetes, but whose function in disease was unknown. They found that the enzyme modifies beta cells' ability to withstand cellular stress and autoimmune killing (7).

"We went on to search for a small molecule that could inhibit renalase function to mimic the protection we observed in cells whose RNLS gene we had inactivated with a mutation," Kissler says. "This search yielded the drug pargyline, which was developed as a treatment for hypertension. Although it is no longer being made, the patent has long since expired, which should make it inexpensive to produce." The team now plan to test the drug in newly diagnosed diabetic patients but, because this drug and others like it are not specifically designed to treat diabetes, questions arise as to the challenges associated with their use.

"Because the drug was originally designed for a different purpose – in this case, the treatment of hypertension – one has to make sure that the original effect of the drug does not pose a safety issue for the new application of the drug," Kissler says.

In the years to come

Whether companies and researchers are pursuing new drugs or repurposing old ones, funding is still vital. Walker says that sustained funding – particularly for those in academic environments – is crucial to making headway in diabetes research.

"High-quality research takes time and, therefore, requires consistent funding to help move it forward," she says. "I have been lucky to have received long-term support, enabling me to build a sustainable program of work. Ultimately, there is a human capital that goes into making research findings and it would be hugely satisfying to take this project to the point where people can benefit."

Although new therapeutic solutions will help inform the future landscape of diabetes management, Mazumdar-Shaw believes that digital therapeutics will also help "achieve optimal outcomes for diabetic patients." These software-driven interventions are currently used across a variety of disease indications to help patients manage the conditions they live with. She says, "Digital therapeutics will emerge as part of the new standard of care for diabetes. By pairing insulin with a digital solution we hope to improve treatment outcomes thus lowering the chances of patients developing co-morbidities, which will reduce costs to healthcare systems in the long term."

The biggest question of all, however, is: will a cure for diabetes be found in our lifetimes? Kissler is optimistic. "It's definitely possible. We all look forward to working on this with optimism, knowing that there may be failures and challenges ahead, but hoping that we can help cure all forms of diabetes as well as their complications."

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Getting the Job (Done)

Sitting Down With…
Will Downie, CEO of Vectura Group, UK

Why business and not science?

After graduating with a degree in biochemistry, I wasn't sure if a life in the lab was for me. There were far better people around who were much more talented in terms of scientific prowess. I saw a job advert for a medical sales rep and thought, why not try that? I was living in Edinburgh at the time. I travelled to London and at the end of the interview, they asked if I had any questions. I naively and brazenly said, "Only one question to be honest. Have I got the job?" After all, I didn't like the idea of traveling home 400 miles without knowing the answer! They sent me back into the reception area while they had a discussion, and ten minutes later they called me back in and offered me a job! I had the option to have territory in either the Highlands of Scotland or Essex. In my mind, the Highlands were cold and rainy, and I didn't know anything about Essex, so I said Essex. I moved from Scotland to London – and I loved it.

What lessons did you learn early in your career?

There is an unwritten rule when you are a medical sales rep: you visit doctors in the morning and you won't be able to see them at any other time. But nobody ever told me that so I would go see them in the afternoons and evenings – and it turned out that I saw more doctors than any of my competitor reps! I really enjoyed the job and I think it worked out because I didn't have preconceptions and I didn't set myself boundaries. I think that mindset is very important in any job. Don't be limited by artificial boundaries. And if you work hard, good things will happen.

From medical sales rep to company CEO… Was it planned?

My career has never been planned! But my rules along the way have always been the same: work hard, try your best, be honest, treat people well, learn as much as you can, and don't be afraid of making mistakes and taking risks.

I've been very fortunate in that I've worked with great companies during my career – and many opportunities have come my way. Like the opportunity with Vectura. From the outside I saw a company with deep scientific expertise and a rich heritage in inhalation drug development that could unlock significant potential if it redirected its efforts into the CDMO industry. The CDMO market today is a very attractive space to be in, especially if you are a company with great technology, world-class innovation and excellent scientists. That's exactly what Vectura is. I've been here eleven months now and I love it.

How did you find the transition to the CEO role?

Previously, I was part of Catalent's executive team. I joined in 2009 and the company went through a huge transformation while I was there – and has been very successful. Catalent is now a very mature company and considered one of the top three players in the space. My role at Catalent was very commercially-focussed, whereas now I am working for a much smaller company in a more generalist role. When you make the transition to CEO, especially in a public company, you need to work with a much broader set of stakeholders, from investors, to shareholders, a board of directors and, of course, all employees in all functions. I must say, I am enjoying the diversity of the role and working with our great team.

And what about the challenges of being a new CEO when the pandemic started?

It felt like the switch for the pandemic was flipped overnight! We'd all heard about the emerging virus but the situation escalated rapidly. There was no playbook to refer to and we huddled together as a leadership team to establish our priorities for the business, with our most important focus being the safety and well-being of our employees. We quickly put in place the measures and operating rhythm we needed to keep the company safe, maintain our quality standards and look after the needs of our customers. From the very beginning, we set up a coronavirus management team that helped us get organized. We kept very close to our teams across all sites and adopted a family-orientated approach to working through every challenge.

What projects are you excited about?

Previously, the company was developing its own pipeline and working with quite a narrow corridor of clients in the respiratory area. Now that we've pivoted to becoming a CDMO, we've opened the aperture of the business and diversified our customers base – we're developing products for a whole range of indications, including asthma, COPD, cystic fibrosis, pulmonary arterial hypertension, lung fibrosis, and COVID-19.

One project that I am particularly excited about is our work with Monash University in Melbourne, Australia. We are working on Oxytocin, which is a standard of care for women during pregnancy to avoid postpartum haemorrhage. In the developed world, women receive the standard of care via injection, but in the developing world it is challenging because the formulation requires cold chain supply and refrigeration, which is clearly a major challenge in hot climates. The number of women who die of postpartum haemorrhage is shocking in developing countries. We are working on the development of a dry powder inhaler version of oxytocin that will not require refrigeration, and may potentially have faster onset of action. It could have a profound impact on women in developing countries.

What is your top advice for other scientists who want to move into commercial roles?

It's your career, so you have to take ownership and find a way to make things happen. Look for new opportunities to try out – ways to expand your experience, such as a secondment position, or a new project, or an entirely new role. And don't be afraid about the transition from science to the commercial world. If you have the right attitude, work hard, and treat people the way you expect to be treated, then good things tend to happen.

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