APRIL 2020 # 64

# the Medicine Maker™



Cambrex

# Your molecule
# Our mission

Drug substance | Drug product | Analytical services


**www.cambrex.com**

# Fragile Pharma?

*As individuals, societies, industries, and governments, we must consider how well prepared we were for this pandemic – and start thinking about the next one*



If you are lucky enough to have avoided the more direct and devastating effects of COVID-19, a "lockdown" may feel almost peaceful – a time for quiet reflection. The one word that comes to my mind when mulling the upheaval caused by the global pandemic is "fragility."

In the modern age of online shopping (next – or even same – day deliveries!), how many of us have considered the need for an emergency stash? A lack of a replaceable food staple is one thing – but what if we can't source medication for a chronic illness? What action do we take when the shelves run truly dry? Globalized supply chains certainly result in reduced prices in developed nations, but what happens when we can no longer import food or medicines? When such support systems start to unravel, the costs will be heavy – and there are no easy answers.

Times like these remind us that risk isn't an abstract concept – life-changing events evidently do happen in our lifetime. Viral outbreaks are not just an overused movie plot. Could we all have been better prepared? This is a question individuals, governments, and industries alike must face. The funding of (rapid) vaccine development is one area that will likely come under increasing scrutiny.

Though we can only commend the scientists and engineers involved in vaccine development for their hard work now and the foreseeable future, the endeavor is reliant on government funding – as Eric von Hofe points out on page 10. He doubts that money is currently in short supply, but does believe that developers could be in a healthier position now, if they had received higher levels of funding in previous outbreaks. Similarly, Andre Kalil, a professor of infectious diseases at the University of Nebraska Medical Center, argued that new therapies were not discovered during the Ebola outbreak because of a lack of randomized controlled trials (1).

Kalil also highlights the unprecedented speed – "from concept to implementation in just a few weeks" – with which trials have been rolled out. The same could be said of Moderna's SARS-CoV-2 vaccine, shipped for trials just 42 days after the genetic sequence was released (2). There may have been missed opportunities with previous outbreaks, but the pace of movement does suggest that some lessons were learned – perhaps pharma isn't so fragile.

Sadly, it sometimes takes a crisis to reveal where the cracks are. And the bigger the crisis, the more cracks we find.

**James Strachan**
*Deputy Editor*

*Reference*

1. *AC Kalil, "Treating COVID-19 – off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics" (2020). Available at https://bit.ly/3bG8HZv.*
2. *Time, "COVID-19 Vaccine Shipped, and Drug Trials Start" (2020). Available at https://bit.ly/2JscaPd.*

# Contents

36



## On The Cover

*Celebrating the most influential people in the pharma industry*

## Upfront



## In My View


## Feature



## NextGen



## Reports



## Sitting Down With





the Medicine Maker

ISSUE 64 - APRIL 2020





Change of address info@themedicinemaker.com
Hayley Atiz, The Medicine Maker, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@themedicinemaker.com
+44 (0) 1565 745 200 | sales@texerepublishing.com

Distribution: The Medicine Maker (ISSN 2055-8201), is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK. Single copy sales £15 (plus postage, cost available on request info@themedicinemaker.com). Non-qualified annual subscription cost is £110 plus postage

*Reprints & Permissions – tracey.nicholls@texerepublishing.com*



texere publishing | Available on the App Store


# Hot Topics at CAR-TCR 2020

**Clinical trial confusion, off-the-shelf cell therapy, 24-hour CAR-T, and more**

In what may have been one of the last advanced therapy meetings to go ahead for some time, delegates met in London in late February for CAR-TCR.

A central theme was the difficulty of conducting clinical trials in Europe compared with the US and China. Dolores Schendel, Medigene, pulled no punches during the first panel discussion of the event, telling the audience that Medigene needed nine academic centers – not the expected three – for a "small phase I trial" in Germany, as well as a "crackerjack" team of lawyers. Schendel suggested that the German situation was a microcosm for the whole of Europe, as different apheresis sites in Germany are regulated by the different states.

Andre Choulika, CEO of Cellectis, also compared the experience of filing a patent in the US to France. "On the US side you had, like, 10 questions. On the French side, you had 16 pages of questions," he said. "It took us 18 months to do this and when you're a small biotech company you're burning cash every month."

The concerns were reflected in the figures presented by Pippa Gledhil from Beacon Intel (see our infographic below) who reported that there were more than five times as many CAR-TCR developers in China and the US compared with Europe.

In terms of other hot topics at the conference, off-the-shelf cell therapy was certainly one – Choulika claimed that 2020 will be the "year of the allogeneic" – as well as TCRs for solid tumors and 24-hour CAR T. But for some allogeneic therapies, there may only be a handful (perhaps less than 50) donors worldwide. Enter the "super donor," whose job it will be to supply the cells needed for such therapies...

Elsewhere, Omar Ali, Visiting Lecturer at the University of Portsmouth and Former Adviser to NICE, spoke about the growth of innovative reimbursement payment models. Here, according to Ali, it is the US that is falling behind because, even if insurers can get their heads around the price, there is ambiguity over who pays when hospitals need more money for administration. "Is it the patient? Is it the government? Is it the insurer? You're driving an electric car with no charge points," he said.

INFOGRAPHIC

# Peeking into the CGT Pipeline

**Intel shows a rise in cell and gene therapy development in the US, with China not far behind**

What are American companies up to?

**6** diseases currently treated with CGT

More than **100** diseases being explored

**362** therapies in development

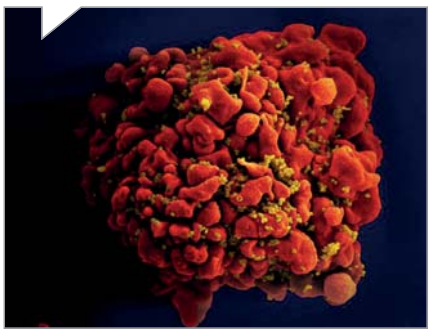
**132** in development for rare diseases

An increase of **25%** since 2018

## ADVANCED MEDICINE IN BRIEF

*Tackling solid tumors with macrophages, a stem cell cure for HIV, and travel bans… What's new in advanced medicine?*

- A proof-of-concept paper has shown that it is possible to genetically engineer macrophages to kill solid tumors in both mouse models and human samples. UPenn researchers were able to overcome the cells' innate resistance to gene transfer with a chimeric adenoviral vector. In addition to expressing CAR, the process transformed the macrophages into highly inflammatory cells that could resist tumor co-option and stimulate the rest of the immune system.
- According to ISCT, the unproven cell therapy market is worth up to a staggering $2.4 billion and involves approximately 60,000 patients annually, paying up to $40,000 per treatment. The society has seen an increase in unproven therapies for COVID-19 and is taking a stand. "Most importantly, these 'treatments' produced with no evidence can be even more dangerous to the immediate health of patients and their communities," said Laertis Ikonomou.
- A major concern for the cell and gene therapy industry is getting around the travel bans that are cropping up in response to the coronavirus pandemic. The good news: Novartis reportedly says it has found alternate methods to ship Kymriah following disruption to passenger flight services from Europe.
- Researchers have used stem cell transplantation in combination with chemotherapy to cure the second-ever patient of HIV. The first patient to be cured nine years ago in Berlin received total body irradiation and two rounds of stem cell transplant from a donor who carried the resistant CCR5Δ32/Δ32 gene, whereas the "London patient" only underwent one round of transplant, a less intensive cocktail of chemotherapy drugs, and no total body irradiation.



## Bug Therapy

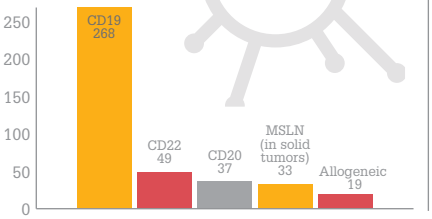
**Cancer patients have responded to a live biotherapeutic–checkpoint inhibitor combo for the first time**

4D Pharma, based in the UK, has partnered with Merck Sharp & Dohme to deliver anti-PD-1 therapy, Keytruda, in combination with a live biotherapeutic to patients with advanced malignancies.

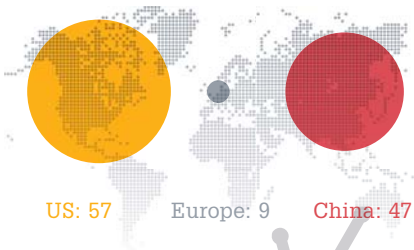
The additional interim clinical data showed two partial responses with evidence of tumor shrinkage; one patient whose disease isn't progressing or regressing, evidence of increased tumor-infiltrating lymphocytes following treatment, and no drug-related serious adverse events.

"Our approach is to take a single strain of bacteria from the human microbiome and understand how it interacts with the immune system. Regarding the strain used in this study, we believe the flagellin protein is responsible for the increased immune activity, which facilitates the activity of the checkpoint inhibitor," says Duncan Peyton, CEO of 4D pharma. "What's interesting is that the two patients in which we saw a response had already received and didn't respond to checkpoint-inhibitor therapy before taking Keytruda in combination with the live biotherapeutic, MRx0518."

A snapshot of the global CAR-TCR landscape: common targets




Global distribution of CAR T Developers




There are **228** CAR/TCR trials in China, which makes up **22%** of the total

*Sources*
*PhRMA, "Medicines in Development 2020 Update: Cell and Gene Therapy" (2020).*
*Beacon Targeted Therapies, "Our Highlights from CAR-TCR Europe 2020) (2020).*

# The Battle Against the Brain-Eating Amoeba

## How can nanoparticles be used to prevent deaths caused by unicellular organisms?

Unicellular organisms like Naegleria fowleri are generally harmless. However, the organism is known by another – far more ominous – name: "brain eating amoeba." N. fowleri typically eat bacteria, but if introduced into humans via nostrils (usually via contaminated water during swimming, ablution, bathing, nasal irrigation etc.) they can use brains as a food source. N. fowleri is attracted to the chemicals that neurons produce when communicating with one another, and will travel through the nose and olfactory nerve before reaching the brain, where it can cause infections like primary amoebic meningoencephalitis (which causes inflammation and destruction of the brain and its linings) and granulomatous amoebic encephalitis (a rare but usually fatal CNS disease).

Though such incidences are fortunately rare, morbidity and mortality rates associated with diseases caused by the amoeba are rising, particularly in developing countries. Now, researchers at the American University of Sharjah, United Arab Emirates, have designed novel compounds which, when combined with silver nanoparticles, show promise in killing the amoeba.

"Currently available antimicrobials can cause severe systemic side effects, such as nephrotoxicity, as they are administered intravenously. And that's one of the reasons why the mortality rate for these diseases is more than 95 percent," says Ruqaiyyah Siddiqui.

Siddiqui and her colleagues tested a variety of quinazolinones and their derivatives in vitro as their antiamoebic effects had not previously been tested. They found that these compounds elicited amoebicidal effects against N. fowleri and Balamuthia mandrillaris, another type of protist pathogen that causes brain infection. The novel compounds alone, as well as in combination with silver nanoparticles, showed potent effects. They also tested the cytopathogenicity and cytotoxicity of the compounds against amoeba-mediated damage of the human keratinocytes, which resulted in the reduced viability of both pathogens.

Siddiqui and Naveed Ahmed Khan, another researcher from the American University of Sharjah, now plan to commence further studies to develop a better understanding of the precise molecular pathways the parasites use to cause disease, with a view to seeking drug targets.

*Reference*

1. *R Siddiqui, "Aryl quinazolinone derivatives as novel therapeutic agents against brain-eating amoebae", ACS Chem. Neurosci, (2020).*

# Sticks and Stones...

## An injectable drug could help heal broken bones faster

Novosteo, a spinout from Purdue University, has developed a targeted drug combination, NOV004, which reportedly helps accelerate the repair of bone fractures and strengthens weakened bones. When injected, the anabolic agents selectively accumulate on bone fracture surfaces where they promote rapid healing. The research team also believes that the localization of the bone-building drug combination at fracture sites will reduce the collateral toxicity that would occur if the agents were to circulate throughout the body.

The company initially intends to focus its use of the product on hip fractures in the elderly, as one in three adults over the age of 60 die within a year of suffering from this type of fracture (1). But Novosteo also has plans to explore the future use of the drug for other applications, including dental implants as well as head and facial fractures.

*Reference*

1. *Purdue University, "Injectable drug for faster healing of bone fractures prepares for clinical trials" (2020). Available at: http://bit.ly/2xaRFUk.*

## IMAGE OF THE MONTH

*Do You See What I See?*

The rise of augmented reality in the pharma industry. IMA Active is using augmented reality for assistance in case of malfunctioning machines.
Credit: IMA Active

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

## QUOTE of the month

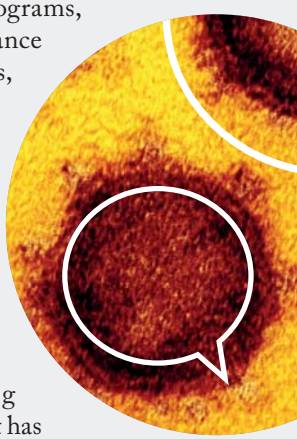
*"Society needs to know it can count on the biopharmaceutical industry to work to rapidly bring forward therapies, vaccines and diagnostics that protect humankind from this escalating pandemic and prepare the industry to better respond to future global health crises".*

Thomas Cueni, IFPMA Director General.
Read more at: https://bit.ly/2wC34fZ

# Pro Bono Advice

**The EMA is offering scientists free advice on the development of therapeutics to treat COVID-19**

Developers of potential therapeutics or vaccines for COVID-19 have been invited to contact the EMA as soon as possible to take advantage of the full fee waiver the agency is offering for fast-tracked scientific advice applications. The agency will identify products mature enough to benefit from the fast-track advice service, which includes preliminary informal comments, feedback on development programs, as well as guidance on best methods, study designs, and the efficacy and safety of products.



In addition to the fast-track scientific advice service, the EMA also reminds drug companies that it has several other measures that can speed up the development of pertinent medicines, including the PRIME scheme (originally launched to enhance support for the development of medicines that target an unmet medical need), accelerated assessment, and conditional marketing authorization procedures.

The EMA is also working closely with other international regulatory bodies to identify effective therapeutics with prophylactic effects.

*Further details are available at: https://bit.ly/2UtZ3ne*

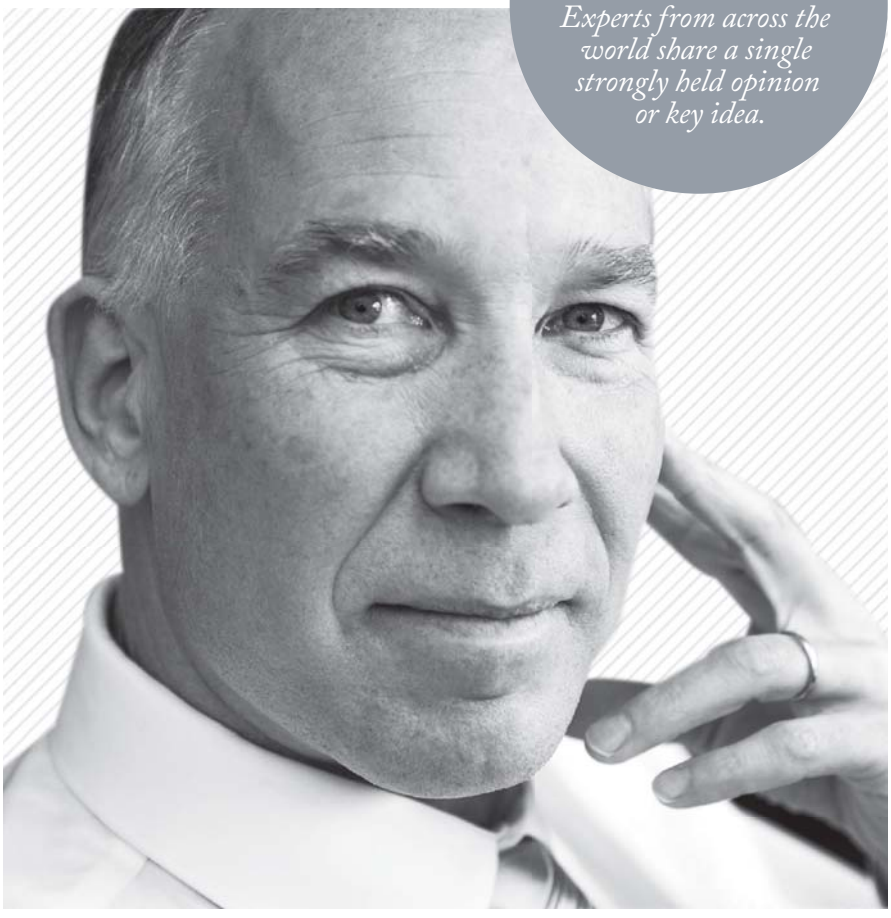
**In My View**

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

# Coronavirus: A Synthetic Solution

## What's the fastest route to a COVID-19 vaccine?

*By Eric von Hofe, CSO at NuGenerex Immuno-Oncology, USA*



The novel coronavirus appears to be less severe in terms of mortality than SARS or avian influenza, averaging about two percent, but it is far more infectious. If too many people contract the virus at once, healthcare systems will not be able to cope with the sudden demand. After the initial wave of infections, there's a good chance that the virus will not go away entirely, and will re-emerge at a later date. There's also the possibility that the virus could mutate into an even more virulent strain. Lastly, it is clear from the emergence of a number of pandemic and potentially pandemic viruses over the last 15 years – from SARS and bird flu to Ebola – that COVID-19 will not be the last. In short, the need for a vaccine to address these threats could not be more pressing.

For the past 20 years, I've been involved in developing immunotherapies for cancer as well as infectious disease. We first began exploring the use of our synthetic peptide technology around 15 years ago when SARS and the avian influenza virus emerged. With avian influenza, in particular, it was nearly impossible to develop a traditional vaccine where you could simply grow large quantities of inactivated virus because the virus would destroy the biological systems needed to manufacture the vaccine. Even if this were successful, developing a traditional vaccine is time consuming.

A much faster approach is to take protein fragments from the virus and use those to stimulate the immune system. These can be manufactured synthetically and do not need to be produced in any biological system, meaning large quantities can be produced quickly. An advantage of our approach is that we modify the peptides, so that they are sure to be recognized by critical components of the immune system.

Previously, we conducted a clinical study with our modified avian influenza peptides, with promising results. We've also found that there's an overlap between the H1N1 swine flu and avian flu in terms of the peptides usable as a vaccine. The result of these studies is that we have identified a process whereby we can, in a relatively short

*"There are basically four novel approaches being taken: DNA, RNA and recombinant protein vaccines, and our synthetic modified peptide approach."*

period of time (roughly three to five months), identify peptides that could be used to immunize people.

There is an 80 percent homology between the novel coronavirus and SARS. We're currently working with another company that specializes in identifying active peptides usable as a vaccine to see if there's an overlap between the peptides we identified in SARS and those in SARS-CoV-2. In addition, computer algorithms have improved significantly in being able to predict active peptides just from the genetic sequence of the virus. The final step is to then take blood cells from people who have recovered from coronavirus and see if they recognize these vaccine peptides. If they do, this is good confirmation that they will make a useful vaccine.

With any infectious disease outbreak, there is generally a great deal of initial interest and funding from governments, particularly if there's the potential for high mortality, until the pandemic passes – and then the funding dries up. Unfortunately, this means that we, as an industry dependent on funding to make advances, are hampered from following through as efficiently as possible in terms of learning what it takes to quickly develop a useful vaccine for a novel agent. It is clear now that the coronavirus is different. It is already having a significant impact on healthcare systems and economies and may well never go away.

I recall that, during the avian flu outbreak, President George Bush Jr announced that the US Federal Government would put $3 billion into research. It seems inevitable that there will be significantly more funding for coronavirus, given the effect it is already having. This time, I believe we will see a more concerted and sustained effort to develop an effective vaccine, as well as a more significant investment in pandemic preparedness.

In terms of where we're at regarding a potential vaccine, there are basically four novel approaches being taken: DNA, RNA and recombinant protein vaccines, and our synthetic modified peptide approach. Trials have started with an RNA vaccine being developed by Moderna. While promising, there are currently no RNA vaccines on the market. We believe that the synthetic approach will be the fastest way to a vaccine but acknowledge that, with unprecedented investment in vaccine development, we may also see some success using more traditional approaches. The main advantage we have is the excellent safety record of peptides in general and our modified peptides in particular. But it is not at all unlikely that some of these novel approaches will be combined.

One thing is for sure: we must not forget the lessons that will be learned over the next year or two because it is inevitable that we will experience something like the new coronavirus again. We must take the learnings from this period and apply them more effectively in the future. My only hope is that we do not have to do too much more learning the hard way.

# Riding China's Regulatory Rapids

**The Chinese market presents a major opportunity for pharma companies, but spending time and money on keeping track of its quickly shifting regulations – as recent changes in the excipients field have shown – is key to success**

*By Matthias Bucerius, Head of Actives & Formulation, Merck*

With the world's largest (aging) population, China provides an enormous opportunity for pharmaceutical companies. Traditionally, the Chinese pharma market has focused on the manufacture of small molecule APIs, but over the past five years, things have changed. Chinese biopharma companies have cropped up and we're seeing an increasing number of global companies investing in China.

Foreign companies, however, can sometimes struggle to navigate the country's regulatory landscape, which has undergone significant changes over the past two decades. Here, I will focus on the regulation of excipients, which, despite a recent shift towards Western standards, is still quite unique (1).

It wasn't until the turn of the century that Chinese regulators first stated in article 11 of the Pharmaceutical Administration Law that excipients should meet certain requirements for medical use. But the general wording

led to inconsistencies, with some provinces regulating excipients as APIs and others not regulating them at all. Then, in 2005, the Chinese FDA introduced a pharma excipient dossier, which proposed excipient registration according to the same process as APIs. And that meant they would be reviewed by the Center of Drug Evaluation (CDE) for import and novel excipients, and by the local CFDA for excipients described in the Chinese Pharmacopeia (ChP). But even this was more of a general principle, with execution and adherence often varying.

Roughly 10 years later, the Chinese State Council initiated substantial reforms for drug approval processes. In 2017, this culminated with the "co-review" or joint review approach. Now, the excipient manufacturer (and no longer the drug manufacturer) is the first party to submit an application of an excipient. The excipient manufacturer then issues a letter of authorization (LOA) with the registration number to the pharmaceutical manufacturer who uses the respective excipient. The pharmaceutical manufacturer then includes the LOA in its dossier when applying for marketing authorization for drugs on the Chinese market.

It was a big change. And although the overall quality framework has dramatically improved over the past 10 years (and is much more comparable to quality systems and standards that we see in the West), the co-review process can be difficult for companies to get their heads around.

When submitting an application through the co-review process, excipient manufacturers must compile a comprehensive dossier to the Chinese authorities for all the excipients they want to commercialize in China. General information on the company and the excipient itself, such as its name, structure, characteristics, approval and usage information must be included. Moreover, detailed information on the manufacturing process is required, together with a list of equipment and process validation data. Lastly, the dossier must include quality control specifications with descriptions of the analytical methods and validation.

*"Detailed information on the manufacturing process is required, together with a list of equipment and process validation data."*

The level of detail required for the registration dossier is based on the excipient classification as revised by the National Medical Products Administration (NMPA, formerly CFDA) in July 2019. Excipients are classified into products with or without a history of use in approved drugs. The latter comprises completely new molecules, as well as molecules with simple changes to their structure or a changed route of administration. Products with a history of use are, in turn, divided into two groups of excipients. The first group includes those excipients that are included in the Chinese Pharmacopoeia or the pharmacopoeias of the EU, the US, UK or Japan. The second group includes those that are not included in these documents.

It's no surprise that a major challenge for companies looking to take advantage of China's emerging biopharma industry is the rapid pace at which regulations change. For example, when the co-review process was introduced in 2017, there was no transition time; to this day, many excipient manufacturers lack the technical dossiers needed for successful registration. As a result, many drug manufacturers cannot yet register their products in China. Another major challenge is that the Chinese Pharmacopeia has not yet been fully harmonized with other international compendia, forcing global pharmaceutical companies to perform additional comparisons of methods and cross-validation checks.

Regulatory developments – and the rise of China's technology and biopharma industries – have shifted public opinion: China is no longer viewed simply as a location for cheap manufacturing. To successfully invest in China, companies should employ the same focus on quality as they would in Germany, the US, or Japan. The fast-growing Chinese pharmaceutical market is highly attractive and holds tremendous potential.

Success requires the investment of time and money – and an ability to understand and navigate China's rapidly evolving regulatory environment. Overcoming the remaining challenges is both rewarding and feasible. And given that the Chinese market is now poised to become even more open, the potential value for international pharmaceutical companies can only increase.

*Reference*

1. *Merck, "Chinese Excipient Regulation – a Globally Unique Challenge" (2019). Available at: https://bit.ly/2U6YUo6*

PDA EUROPE

# Event Outlook

**Quality and Regulations**
JUNE 2020

**BioManufacturing**
SEPTEMBER 2020

**Medical Devices and Digital Healthcare**
SEPTEMBER 2020

**Aseptic Animal Health**
OCTOBER 2020

| 2020 | | |
|---|---|---|
| 9-11 June | Quality and Regulations Conference | Virtual Conference |
| 22-23 June | Virus Forum | Virtual Conference |
| 24-25 June | Advanced Therapy Medicinal Products | Virtual Conference |
| 8-9 September | Medical Devices and Digital Healthcare | Madrid, Spain |
| 22-23 September | BioManufacturing | Dublin, Ireland |
| 24 September | Pharmaceutical Freeze Drying Technology | Dublin, Ireland |
| 19-20 October | Visual Inspection Forum | Berlin, Germany |
| 20-21 October | Aseptic Animal Health | The Hague, The Netherlands |
| **2021** | | |
| 5-6 October | The Universe of Pre-Filled Syringes and injection Devices | Gothenburg, Sweden |

CONNECTING PEOPLE SCIENCE AND REGULATION®

# The Rise of Lipid Nanoparticles

**Lipid nanoparticles (LNPs) are typically seen as a niche approach to formulation, but with more complex molecules filling company pipelines, is it time for LNPs to finally shine? Rahul Keswani and Benjamin King are formulators at Exelead specializing in early stage LNP development. We asked for their take on the current market for LNPs.**


### Why are LNPs so compelling for certain drug molecules?

Many of today's drug molecules are small molecules and biologics, but increasingly there is a move beyond traditional biopharmaceuticals to more specialized and complex therapies. These include oligonucleotides — including RNA, mRNA, siRNA, and even DNA-based molecules — that can trigger an effect at the genetic level to combat disease. As one example, a drug molecule could include siRNA to inhibit expression from messenger RNA (mRNA) in cells to enable therapeutic activity. Drug products are also being developed that deliver mRNA to a cell to provide expression of therapeutic proteins.

LNPs are receiving increasing attention in the industry because of their ability to act as drug carriers for these complex but highly promising therapeutics. Oligonucleotides are susceptible to degradation in the body, but LNPs provide a stable matrix for the drug molecule to reside in. They can also facilitate entry into target cells.

One common misconception is that liposomes and LNPs are interchangeable terms. They are similar — and both can be effective for drug delivery — but liposomes are simpler vesicular formulations made up of a mostly aqueous interior core. Liposomes for drug delivery were developed in the 1970s. LNPs can be seen as a new generation of liposomes that have a more complex internal lipid architecture with low or minimal internal aqueous presence that is well suited to stable and efficient encapsulation of various genetic payloads.

### Are companies reluctant to use LNPs?

LNPs are not the go-to formulation approach for routine pharmaceutical development; they are better suited to highly complex APIs, such as those based on oligonucleotides or products requiring unique biodistribution profiles or delivering multiple payloads. These types of therapies are appearing more frequently in drug development pipelines as companies focus more on identifying druggable targets at the genetic level. Because of this growing activity, the LNP market is set to expand significantly in the coming years. The main advantages of LNPs are improved stability and delivery efficiency for oligonucleotide APIs. Simply put, the API is much less likely to degrade before it can deliver its therapeutic effect because it is protected by the by the LNP. Moreover, the LNP can be specifically targeted using customized ligands attached to its surface.

Drug developers can be wary of LNPs because of the perceived complexity — and they are certainly more involved formulations than the industry is typically used to! But this is where companies like Exelead come in. We do the heavy lifting to help clients reap the benefits of LNP formulations to create effective oligonucleotide-based medicines. We find that clients are often pleasantly surprised at the flexibility these platforms can offer. For example, the library of lipid excipients that can be used in these formulations is sizeable, and it is growing rapidly with the current interest in oligonucleotide-based therapies.

### What are the main challenges of working with LNP formulations?

Synthesizing nanoparticles is a complex process, and requires a different sort of formulation expertise compared to traditional fill-finish activities for parenteral products where the API is essentially combined with a mixture of buffer and excipient ingredients. With LNPs, you need a good understanding of exactly how to mix the molecules; flow rates, temperatures, composition, and component ratios are all crucial to influence formation of the nanoparticles and efficiently encapsulate the API.

Other challenges relate to filterability and stability. LNP formulations need careful optimization of the filtration to achieve high flux and throughput while also maintaining the nanoparticulate morphology. While

there is always an option to synthesize the formulation in an aseptic environment, the process becomes very challenging and expensive. Again, developing a good understanding of the design space, and how design variables impact product attributes such as encapsulation, nanoparticle diameter, and formulation stability can help set you up for success at sterile filtration as well.

It is also worth noting that LNPs demand extra attention in the supply chain in terms of getting all of the different raw materials ready at the same time – and made to cGMP standards. However, the growing interest and investment in oligonucleotides has led to significantly more research in the area – including how to make and modify LNPs. Often, just changing a few ingredients can lead to enormous benefits. The additional know-how and development to optimize these variables are well worth the effort. Oligonucleotides are becoming a go-to approach to tackling disease, and LNPs go hand in hand with them, ensuring that the best therapeutic benefit currently possible reaches the precise location where it is most effective. When these processes can be made scalable and easily transferable to many different kinds of products, it becomes clear that the technology is becoming truly relevant, and more important to the overall pharmaceutical market. And that's where we are with LNPs right now.

After years of R&D, the first siRNA-based therapy, patisiran, was approved in the US in 2018 for the treatment of a rare form of hereditary peripheral nerve disease – and it uses an LNP formulation. The drug inhibits the expression of an abnormal protein by interfering with the segment of RNA that creates it. Patisiran is just the first approved drug; many more oligonucleotides using LNPs are in pipelines and clinical trials.

What is your advice for companies interested in pursuing LNP formulations?

Our guiding principle, and advice to any company, is to always consider scalability from the very start. Clients often come to us with a product in the early stages of development that they wish to scale up, but it's clear they have not fully considered its feasibility. It is never too early in your development process to start thinking about paths to scale-up. We would even go so far as to recommend looking at developing with unit operations that are scaled down from manufacturing scales to bench scales rather than developing a bench scale process and trying to fit into manufacturing scale after-the-fact.

At Exelead, we've been working with LNPs for years, so we have the technology and expertise to improve the LNP formulation process, and develop a more scalable format. We've been able to form the same particles seen in the client's early stage process using a much more scalable method, such as in-line mixing (a simple ratio matrix mixing involving the right ingredients, pH and temperature) or, in some cases, extrusion (although the latter is not typically suitable for oligonucleotides, which tend to be shear sensitive). We can help clients with formulation development wherein we can suggest lipid choices and potential vendors based on desired pharmacological performance, develop these formulations at bench-scale volumes (<20 ml) rapidly within a short time-frame and provide a bank of potential candidate formulations for use in their screening assays. When we execute these pseudo-high-throughput approaches to development, we are able to present a panel of options to a client who can then select a candidate based on fulfillment of their desired quality attributes. We also use tangential flow filtration to remove organic solvents, which is a low-cost unit operation.

What other expertise does Exelead bring to LNP development?

Nanomedicinal formulations require careful attention to detail, comprehensive expertise and complementary teams to design and manufacture successful products. Exelead's primary expertise is in parenteral drug products focused on LNP/liposomal formulations and PEGylated (polyethylene glycol) formulations.

We have more than 150 employees from diverse backgrounds and areas of expertise, and we offer end-to-end solutions to our customers — from pre-clinical development through commercial supply, from project management to stability testing. We offer considerable support for nanoparticle formulation development and optimization, using lipids, polymers and other traditional ingredients.

Currently, the pharmaceutical industry is seeing an explosive growth in the oligonucleotide market, particularly with hard-to-treat diseases. Our development teams can help scale up manufacturing processes to support commercial production, and our in-house analytical capabilities involve the whole spectrum of specialized assays for the lipids, particle size and surface charge, residual solvents, and APIs required to release a product.

By offering end-to-end solutions, a dedicated team with deep expertise and a robust cold chain, Exelead clients can expect to reduce supply chain risks and proceed with confidence. With our multi-decade history and proficiency with complex formulations, Exelead is uniquely poised to support clients who wish to bring exciting new treatments to the clinic and market.


# CELEBRATING THE GREAT MINDS THAT BRING US INNOVATION IN SMALL MOLECULES, BIOPHARMACEUTICALS, AND ADVANCED MEDICINE

2020 has proven to be a challenging year for humanity: volcanic eruptions, bushfires, floods, storms, the melting of glaciers, and the emergence of COVID-19, which has brought much of the world to a standstill. Against this backdrop, putting together The Medicine Maker's annual Power List has been a surreal experience. How can we prepare for a celebration of pharmaceutical development and manufacturing when it seems as if the world is falling apart around us? At times like this, we believe it is even more important to recognize the many people working hard to improve our world. The professionals highlighted here are driving the industry forward and saving lives by developing new medicines. And some of these professionals will also be lending a helping hand in bringing COVID-19 vaccines and treatments to market as soon as possible.

For 2020, we present the top 20 inspirational medicine makers in three different categories: Biopharmaceuticals (page 17), Advanced Medicine (page 22), and Small Molecules (page 28).

*By Stephanie Sutton, James Strachan, and Maryam Mahdi*

# BIOPHARMACEUTICALS

## Top 20

### HAL BASEMAN

CHIEF OPERATING OFFICER AT VALSOURCE

"Given the relatively slow pace of innovation in biopharmaceutical manufacturing technology, our industry needs to consider more effective ways to employ innovative methods and technologies. We need to recognize where traditional methods and ways may no longer be the best. We need to identify where innovation can improve the manufacturing process and quality assurance. Then, we must use this information as motivation to work with suppliers and regulators to develop and implement those technologies. This recognition that there will likely be a need for inclusion of new technology should be addressed in the plans for manufacturing processes and facilities – even and especially where that new technology may not be apparent."

### ROBERT BRADWAY

CHAIR AND CHIEF EXECUTIVE OFFICER AT AMGEN

Prior to Amgen, Bradway was a managing director at Morgan Stanley in London. He joined Amgen in 2006, becoming Chair in 2013 and CEO in 2010. He is also the chair of the CEO Roundtable on Cancer, a non-profit organization of executives that focuses on solutions to cancer treatment and prevention, and a member of the American Heart Association CEO Roundtable.

Amgen and the Amgen Foundation recently committed $12.5 million to support COVID-19 relief efforts.

### RICK BRIGHT

DIRECTOR AT THE BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORIT (BARDA); AND DEPUTY ASSISTANT SECRETARY IN THE OFFICE OF THE ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE AT THE US DEPARTMENT OF HEALTH AND HUMAN SERVICES

Bright is an expert on immunology and influenza – and previously served as Director of the Influenza and Emerging Infectious Diseases Division in BARDA. "While I was at the CDC, I developed a rapid screening tool to assess antiviral drug resistance in influenza viruses. Using the tool, I discovered that all circulating influenza viruses were resistant to the world's most used influenza antiviral drug. This led to CDC guidance change on the use of influenza antiviral drugs. As BARDA director, I changed the USG strategy to drive and incorporate innovation to improve our nation's health security and pandemic response posture," he says.

Bright is currently working to implement a strategy for improved pandemic response capabilities throughout the SARS-CoV-2 pandemic.

## DARIO CAMPANA

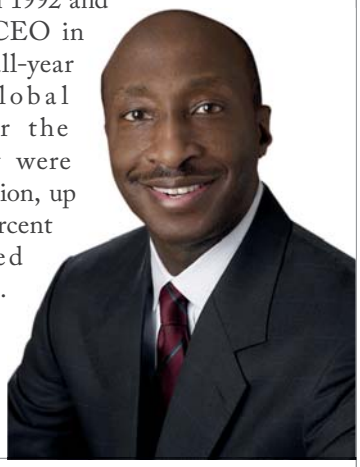
MRS. LEE KONG CHIAN CHAIR IN ADVANCED CELLULAR THERAPY AND PROFESSOR, DEPARTMENT OF PAEDIATRICS, AT THE NATIONAL UNIVERSITY OF SINGAPORE

"The defining event of my career was discovering a passion for translational research during my laboratory training. Subsequently, there was guidance from a multitude of indirect mentors, and inspiration from patients."

## KENNETH C. FRAZIER

CHAIR AND CHIEF EXECUTIVE OFFICER AT MERCK SHARP & DOHME

Frazier started out as a lawyer and taught trial advocacy in South Africa. He joined MSD's public affairs division as a general counsel in 1992 and became CEO in 2011. Full-year 2019 global sales for the company were $46.8 billion, up by 11 percent compared with 2018.



## MIKE GRIPPO

SENIOR VICE PRESIDENT, STRATEGY & CORPORATE AT CATALENT PHARMA SOLUTIONS

"The cost and complexity of bringing a biologic to market can be daunting, especially when the 'burn rate' of small biotech companies can exceed $250,000 per week, and 9 out of 10 drugs in clinical trials never make it to market. By providing integrated, end-to-end solutions, we help customers overcome development hurdles. It's more important than ever that we demonstrate advantage at every stage, and save innovators the costs and delays of negotiating with multiple contractors, and the complexity and risks of handoffs and tech transfers."

## JACKIE HUNTER

CHIEF EXECUTIVE OFFICER AT BENEVOLENTBIO; AND CE OF CLINICAL AND STRATEGIC PARTNERSHIPS AT BENEVOLENTAI

BenevolentAI is using artificial intelligence technology to transform the way medicines are discovered and brought to market. Jackie Hunter has extensive experience in the industry and was previously responsible for developing GSK's external innovation strategy, as well as the concept of the Stevenage Bioscience Catalyst. In 2010, she was awarded a CBE in the Queen's Birthday Honours list in the UK for Services to the Pharmaceutical Industry.

## JUSTIN HANES

LEWIS J. ORT PROFESSOR OF OPHTHALMOLOGY AT JOHN HOPKINS UNIVERSITY

"If I could do one thing to improve the positive impact of drug development and the biopharma industry, it would be to dramatically increase funding for basic medical science, starting with the National Institutes of Health in the US and its counterparts throughout the world, filling the pipelines of existing companies, and leading to the creation of hundreds of startups with more effective new drugs and vaccines."

## MARIA JOSÉ ALONSO

PROFESSOR OF BIOPHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY AT THE UNIVERSITY OF SANTIAGO DE COMPOSTELA

"A defining moment for me was my postdoctoral training with Robert Langer at MIT, who introduced me to the global health area of research. This impacted my career and opened the door for collaborations with the Bill and Melinda Gates Foundation and the World Health Organization."

Maria José Alonso's lab has pioneered numerous discoveries in nanomedicines and she is also a past president of the Controlled Release Society. She believes that drug development could improve if academic researches adopt a more "rational approach towards unmet needs and criteria to ensure quality and reproducibility".

## RICHARD JOHNSON

PRESIDENT AND CHIEF EXECUTIVE OFFICER AT THE PARENTERAL DRUG ASSOCIATION (PDA)

Johnson joined the PDA as President in 2009, following a 30-year career in the pharma industry, which included 20 years as an active PDA volunteer and member. Early in his career, he took on international assignments, which he says changed his perspective and prepared him for the globalization of the industry. "Right now, our industry has dual responsibilities in the fight against the COVID-19 global pandemic: one, continuing the supply of critical medications while dealing with supply chain interruptions, personnel absenteeism, and societal impacts; and two, rapidly developing and evaluating treatments and vaccines to combat COVID-19."

## KIRAN MAZUMDAR-SHAW

CHAIR AND MANAGING DIRECTOR, BIOCON

Although initially intending to be brewmaster, Mazumdar-Shaw set up an entrepreneurial biotechnology company in India in the 1970s. Since then, Biocon has grown to become a globally recognized company and Mazumdar-Shaw has received numerous awards and honors. In November 2019, she received a Lifetime Achievement Award from the Indian Council of Medical Research for outstanding achievement in healthcare and contribution to the society at large.

## MAIK JORNITZ

PRESIDENT AND CHIEF EXECUTIVE OFFICER AT G-CON

"Joining the PDA turned out to be a huge turning point for my career. It opened up a large network of peers for me; peers I can learn from and that I can tap into the experience of when needed and vice versa. Moreover, it is a joy to work together with this group of experts to support our industry, regulators, and suppliers. I have learned that when we all work together, we can accomplish phenomenal benefits for our industry and patients. Right now, there are new therapies – in some instances, cures – entering late-stage development phases rapidly, and showing extremely encouraging signs. Patients who could not be helped in the past have a good chance of treatment and survival. This is extremely motivating!"

## RINO RAPPUOLI

CHIEF SCIENTIST AND HEAD, EXTERNAL R&D AT GLAXOSMITHKLINE

Rappuoli is considered one of the world's leading vaccine experts. He was involved in the development of CRM197 used in H. influenzae, N. meningitidis, and pneumococcus vaccines, and has also introduced several novel scientific concepts – genetic detoxification (1987), cellular microbiology (1996), reverse vaccinology (2000) and the pangenome (2005). He is now involved in collaborations focusing on a vaccine for COVID-19.

## MIKE REA

CHIEF EXECUTIVE OFFICER, IDEA PHARMA

Mike Rea says that the biggest course change in his career was leaving a job because he didn't agree with their strategy. Without that, he'd never have started IDEA Pharma - a consultancy focusing on path-to-market design strategies. When it comes to improving biopharma development, Rea believes that less managerialism, combined with organizations taking more of the right kinds of risk in early-phase development, would improve decision quality.

## LUC-ALAIN SAVOY

GLOBAL HEAD OF BIOLOGICS – LIFE SCIENCES AT SGS

Luc-Alain Savoy was the managing director of M-Scan SA, which focused on protein characterization, bioanalysis, and impurities in identification and quantification before it was sold to SGS in 2010. "Joining SGS Life Sciences gave me the opportunity to convey my ideas and values to a larger audience of biopharma decision-makers," he says. For the future, he is passionate about access to medicine – and hopes to see more affordable biological drugs being made available to the whole population.

## MELINDA RICHTER

GLOBAL HEAD OF JLABS AT JOHNSON & JOHNSON INNOVATION

"Improving access to medicines starts with shortening the amount of time it takes to get a therapeutic into the hands of the patient or consumer. Typically, that process can take up to ten years and millions or even billions of dollars. This has to change!" Before joining JLABS, Richter was the Founder and CEO of Prescience International, which was dedicated to accelerating research to the patient. Richter created the company after a medical emergency left her questioning the efficiency of the current healthcare system. In her current role, she supports the innovation community by creating capital-efficient commercialization models that help early-stage companies.

## CARLO TONIATTI

CHIEF SCIENTIFIC OFFICER AT IRBM

"I envisage that a major breakthrough in drug development will come from technological advancements. In particular, the more extensive generation and use of big data originating from preclinical and clinical studies, combined with a more comprehensive application of artificial intelligence-enabled solutions. This will cover all the steps of drug discovery and development, from the initial target identification to clinical trial design and data interpretation."

## JAMES N. THOMAS

EVP, GLOBAL HEAD OF BIOTHERAPEUTICS AND PRESIDENT OF US OPERATIONS AT JUST - EVOTEC BIOLOGICS

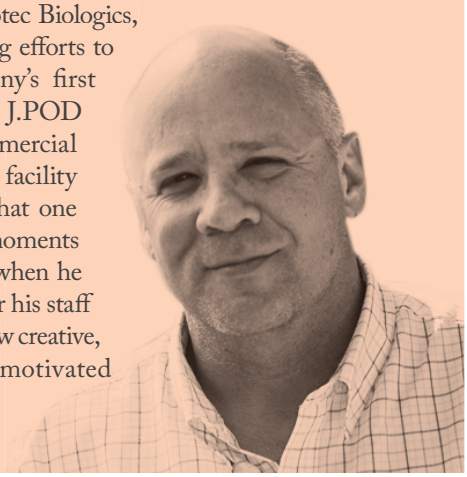
Over the course of his career, Thomas has contributed to the advancement of many important therapeutics including Activase, Vectibix, Enbrel, Prolia/Xgeva and Repatha, as well as numerous biosimilar programs. Thomas has built teams, departments, and functions passionate about creating and using innovative technologies to meet the needs of patients. In 2014, he co-founded and became CEO of Just Biotherapeutics, with a focus on expanding global access to biologics, and is now continuing this journey at Just-Evotec Biologics.

## MIKE VANDIVER

SENIOR VICE PRESIDENT OF BIOTHERAPEUTIC OPERATIONS AT JUST - EVOTEC BIOLOGICS

Vandiver has over 30 years of biopharmaceutical process development and manufacturing experience. At Just Biotherapeutics, he led efforts to bring the company's clinical GMP facility online.

Now at Just - Evotec Biologics, Vandiver is leading efforts to bring the company's first North American J.POD clinical and commercial biomanufacturing facility online. He says that one of the defining moments of his career was when he started to empower his staff and learned just how creative, innovative, and motivated they could be.



## EMMA WALMSLEY

CHIEF EXECUTIVE OFFICER AT GLAXOSMITHKLINE

Walmsley first joined GSK in 2010, initially working for the Consumer Healthcare, Europe, division. She became CEO in April 2017. 2019 was seen as a strong year for the company, with an increase in group sales, eight filings, six positive pivotal trial results, and four priority assets moving to phase II/III.

# ADVANCED MEDICINE

## *Top 20*

### USMAN "OZ" AZAM

PRESIDENT AND CHIEF EXECUTIVE OFFICER AT TMUNITY THERAPEUTICS

As head of cell and gene therapy at Novartis between 2014 and 2016, Azam was part of the team that brought the first CAR T cell therapy to market. Before that, he held various science, regulatory and commercial roles at Aspreva, J&J and GSK — originally training as an obstetrician and gynecologist. At Tmunity, Azam is focused on bringing the next-generation of T cell therapies to market.

### VERED CAPLAN

CHIEF EXECUTIVE OFFICER AT ORGENESIS

Orgenesis is building a network of hospitals around the world called point of care (POCare), which are equipped to develop and process cell and gene therapies. "Instead of frantically searching for ways to turn a few chosen therapies into off-the-shelf products and generate quick profits for mammoth biotech companies ruled by the ruthless demands of short-term economic and stock market pressures, our challenge is to advance towards a more decentralized healthcare integrated industry – a truly consumer-based industry."

### MASSIMO DOMINICI

ASSOCIATE PROFESSOR OF MEDICAL ONCOLOGY AT THE UNIVERSITY HOSPITAL OF MODENA AND REGGIO EMILIA

"My ultimate vision is allogeneic cell production centralized within large-scale manufacturing models, where the last steps of cell product reconstitution/manufacturing are performed at the hospital level, in a solvent/solute model – as we already see with chemotherapy agents. This would require a chain of trust between pharma and caregivers and must be facilitated by novel culture technologies, breakthrough cryobiology innovations, new packaging and dedicated infusion systems."

### JENNIFER DOUDNA

PROFESSOR OF BIOCHEMISTRY, BIOPHYSICS AND STRUCTURALBIOLOGY AT THE UNIVERSITY OF CALIFORNIA, BERKELEY

Early in her career, Doudna's lab determined some of the first crystal structures of RNA and RNA-protein complexes. In 2012, she rose to fame after co-discovering the revolutionary gene editing technology, CRISPR-Cas9. She later co-founded Caribou to commercialize the technology. Recently, Doudna's team created a COVID-19 diagnostic lab from scratch, with the capability to process more than 1,000 patient samples per day.

## MIGUEL FORTE

CHIEF EXECUTIVE OFFICER AT BONE THERAPEUTICS

"Advanced therapies represent a real opportunity for long-term effect and even cures for many currently unmet medical needs. I believe we will progressively increase our capacity to cost-effectively and consistently produce advanced therapies. More than 10 years ago when I started my involvement with cell therapy, the field was delivering promise, but today we all agree it is delivering value. Tomorrow it will provide cures that are unthinkable even today!"

## KURT GUNTER

CHIEF MEDICAL OFFICER AT KUUR THERAPEUTICS

Kurt Gunter has an expansive history in advanced medicine, spanning many roles. After starting his career as a physician, he went into regulation – becoming deputy director of the FDA's cellular and gene therapy division in 1988. Then, after heading up stem cell processing at the Children's National Medical Center, he took several leadership positions in industry (including Transkaryotic, ViaCell and Hospira). He is an active member of many societies, and has served as President of ISCT.

## DENG HONGKUI

CHANGJIANG PROFESSOR, THE BOYA CHAIR PROFESSOR, AND DIRECTOR OF THE INSTITUTE OF STEM CELL RESEARCH AT PEKING UNIVERSITY

In 1989, Deng Hongkui left China for the US, working on HIV at New York University before switching to stem cells – eventually becoming research director of the stem cell company ViaCell in Cambridge, Massachusetts. He then went back to China after being awarded the prestigious Changjiang Professorship. In 2017, he and Chen Hu engineered resistance to HIV in mice using CRISPR gene editing, and for the first time used the technique on an AIDS patient – demonstrating the safety of CRISPR for humans.

## RACHEL HAURWITZ

CHIEF EXECUTIVE OFFICER AT CARIBOU BIOSCIENCES

Haurwitz has a research background in CRISPR-Cas biology and holds several patents covering CRISPR-derived technologies. She co-founded Caribou in 2012 and Intellia Therapeutics in 2014, both of which are developing genome editing therapies. Late in 2019, Caribou published a paper showing that their type I CRISPR-Cas platform, FokI-Cascade, can be used to perform genome editing with high precision.

## QUEENIE JANG

CHIEF EXECUTIVE OFFICER AT THE INTERNATIONAL SOCIETY FOR CELL AND GENE THERAPY (ISCT)

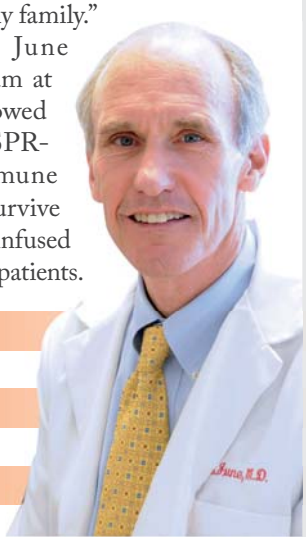
Jang thinks the emergence of the advanced medicine field is akin to evolution from analogue to digital platforms in the IT sector. She also believes that cost-of-goods optimization is key to broad healthcare adoption of ATMPs. "This will create higher demand for technical expertise to execute on product development plans as the CGT sector rapidly expands. Therefore, training and development to populate this highly skilled CGT workforce will become critical to fuel growth of the sector."

## CARL H. JUNE

RICHARD W. VAGUE PROFESSOR IN IMMUNOTHERAPY AT THE UNIVERSITY OF PENNSYLVANIA

Carl June's research was pivotal to the development of CAR T cell therapy. In 2018, he was named as one of Time Magazine's most influential people. His entry was written by Emily Whitehead, aged 12, who was the first patient to receive CAR T cell therapy six years earlier. "Dr. June is my hero! He saved my family."

Recently, June and his team at UPenn showed that CRISPR-edited immune cells can survive after being infused into cancer patients.



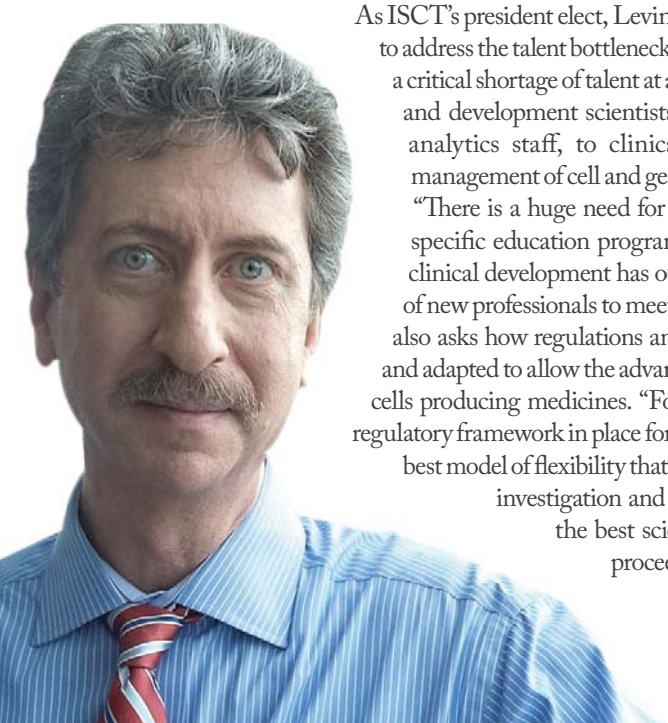
## PETER MARKS

DIRECTOR OF THE CENTER FOR BIOLOGICS EVALUATION AND RESEARCH AT THE FDA

During his wide-ranging career, Peter Marks has been involved in practicing internal medicine and clinical science with Brigham and Women's Hospital in Boston, academic medicine at Yale (where he led the adult leukemia service), pharmaceutical drug development, and most recently, regulation. As head director of CBER, Peter plays a pivotal role in the development and commercialization of advanced medicines in the US.

## BRUCE LEVINE

BARBARA AND EDWARD NETTER PROFESSOR IN CANCER GENE THERAPY AT THE UNIVERSITY OF PENNSYLVANIA



As ISCT's president elect, Levine has been vocal about the need to address the talent bottleneck in advanced medicine. "There is a critical shortage of talent at all levels, from technicians and development scientists, manufacturing and analytics staff, to clinical expertise in the management of cell and gene patients," he says. "There is a huge need for more cell and gene specific education programs as scientific and clinical development has outpaced the training of new professionals to meet the demand." Levine also asks how regulations and policies can be revised and adapted to allow the advancement of cells and engineered cells producing medicines. "For countries that have a limited regulatory framework in place for advanced therapies, what is the best model of flexibility that protects patients while allowing investigation and subsequent approvals based on the best scientific and clinical evidence to proceed?" he asks.

## ANTONIOS MIKOS

PROFESSOR AND DIRECTOR OF THE CENTER FOR ENGINEERING COMPLEX TISSUES AT RICE UNIVERSITY

"A major obstacle for tissue engineering is the translation of biological discoveries into regenerative medicine solutions for the treatment of patients," says Mikos. His vision for advanced medicine focuses on the development of biomaterials to enable engineers, scientists, and clinicians to work collaboratively to create viable tissues and organs. "I am confident that the convergence of sciences will address some of society's toughest healthcare problems."

**RODGER NOVAK**

CO-FOUNDER AND PRESIDENT AT CRISPR THERAPEUTICS

Novak is one of the three co-founders of CRISPR Therapeutics, which aims to treat diseases using CRISPR/Cas9 gene editing technology. In 2019, the company announced positive interim safety and efficacy data in their ongoing CTX001 clinical trials, a CRISPR/Cas9 therapy for β-thalassemia and sickle cell disease, as well as advancing their first allogeneic CAR T cell therapy targeting CD19+ malignancies.

**QASIM RAFIQ**

ASSOCIATE PROFESSOR IN CELL AND GENE THERAPY BIOPROCESS ENGINEERING AT UNIVERSITY COLLEGE LONDON

"As a biochemical engineer by training, I would expect the delivery of cell and gene therapies to be underpinned by robust and scalable bioprocesses and innovative manufacturing technologies. To ensure the sector's continued growth, it is now at a critical juncture where it needs to demonstrate sustained value and commercial viability. This can only be achieved through improved standardized, scalable and robust manufacturing processes. In brief, advanced therapies need to be industrialized."

## JOHN ROSSI

DIRECTOR OF TRANSLATIONAL SCIENCES AT KITE PHARMA

"I believe in my heart of hearts that we are going to use off-the-shelf progenitor stem cells engineered to target cancer cells and overcome the tumor microenvironment. Off-the-shelf therapies will reduce costs and increase access to a great number of patients. It will take time, but it's where we are headed – Kite has an active program in that area. It is also crucial that we continue to invest in academic science that seeks further advances. Kite is sponsoring numerous studies, providing funding and samples to some of the best and brightest in the field. We hope that governments around the world will continue to invest in basic research that is ultimately going to drive these next generation therapies."

## DOLORES SCHENDEL

CHIEF EXECUTIVE OFFICER AND CHIEF SCIENTIFIC OFFICER AT MEDIGENE

Schendel has been a member of the German Research Foundation, German Cancer Aid and the European Research Council, and developed her interest in tumor immunology while working at the Sloan-Kettering Institute in New York. In 2019, Medigene commenced a phase I/II trial of its first TCR-T immunotherapy against several blood cancers.

## CLAUDIA ZYLBERBERG

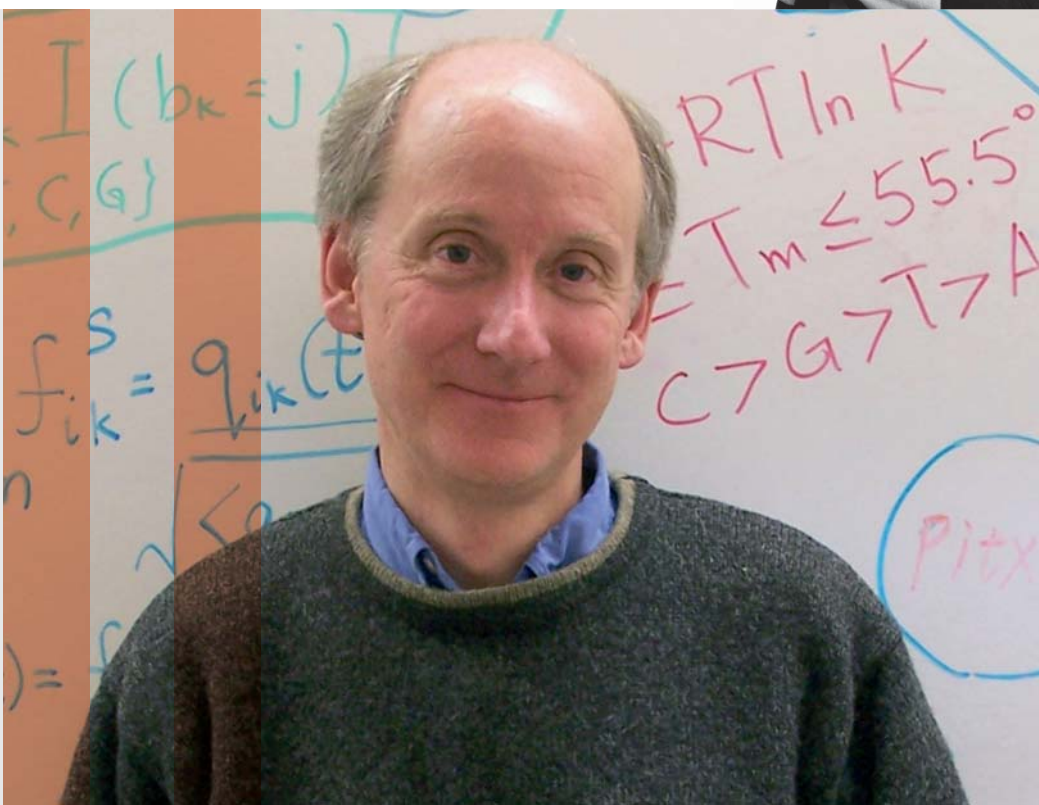
CHIEF EXECUTIVE OFFICER AT AKRON BIOTECHNOLOGY

Zylberberg is concerned about the lack of closed or automated systems in cell and gene therapy. "The closing of systems will provide opportunities to manufacture in different environments, such as hospitals, and will enhance the capability to scale-out many of these autologous therapies. Right now, you would need a CMO to manufacture them, but a closed system would allow you to manufacture anywhere. The logistics, globally, of these therapies is also one of the biggest pieces of the puzzle." Akron has responded to the COVID-19 epidemic by offering its biomolecules, such as interferons and other novel formulations, to be further investigated. "These will hopefully be used to create solutions for early stages of infection and advance initiatives that we've proposed both independently and in collaboration with others."

## JAMES THOMSON

INVESTIGATOR, REGENERATIVE BIOLOGY AT THE MORGRIDGE INSTITUTE FOR RESEARCH

James Thomson is a developmental biologist well known for his pioneering work isolating and culturing human embryonic stem cells in 1998, and developing human pluripotent stem cells from adult skin cells in 2007. He co-founded Cellular Dynamics International (now part of Fujifilm) in 2004 to commercialize human-induced pluripotent stem cells for drug discovery and toxicity testing. In 2019, the Thomson Lab at Morgridge found a better way to grow smooth muscle cells from pluripotent stem cells.



**SHINYA YAMANAKA**

DIRECTOR AND PROFESSOR AT THE CENTER FOR IPS CELL RESEARCH AND APPLICATION (CIRA) AT KYOTO UNIVERSITY

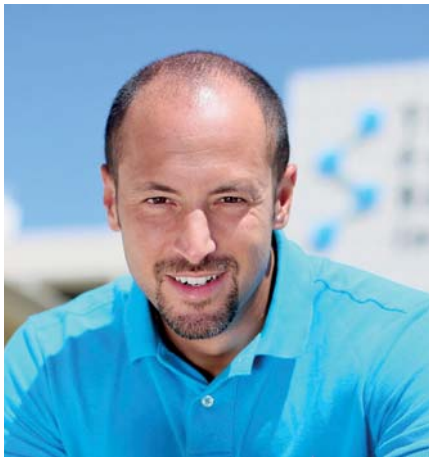
Shinya Yamanaka believes the number one obstacle for advanced therapies is time and cost. “It could take decades and hundreds of millions of dollars to bring a breakthrough in basic research to patients,” he says. “How to survive this long and costly journey is the biggest hurdle.” Yamanaka believes the current goal in his field of regenerative medicine is to reactivate patients’ own regenerating potentials by small molecules or other means, without transplanting cells from outside.

# SMALL MOLECULES

## Top 20

### PHIL BARAN

PROFESSOR AT SCRIPPS RESEARCH



Phil Baran has received numerous awards and accolades for his contributions to both industry and academia. He has worked at the Scripps Research Institute since 2003 and says he is most inspired by his "former mentors, students and postdoctoral collaborators", as well as entrepreneur Elon Musk. His research interests include the organic synthesis of complex molecules with minimal labor and material costs.

### MINZHANG CHEN

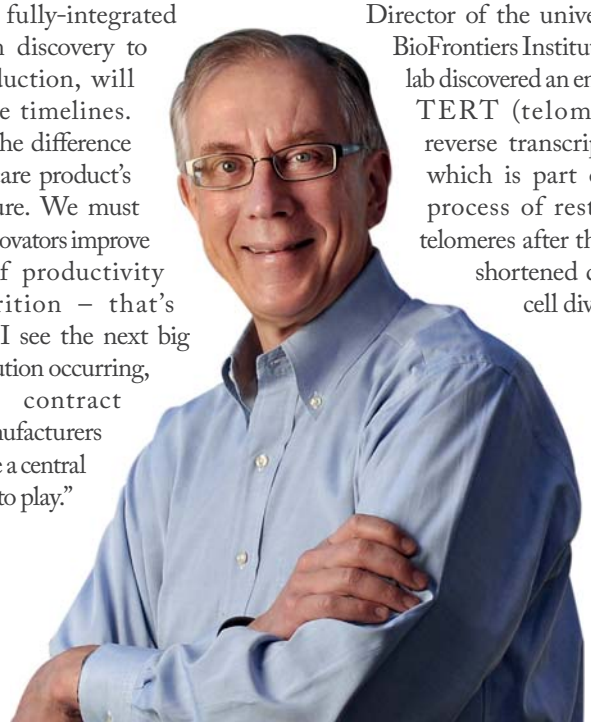
CHIEF EXECUTIVE OFFICER AT WUXI STA, A WUXI APPTEC COMPANY

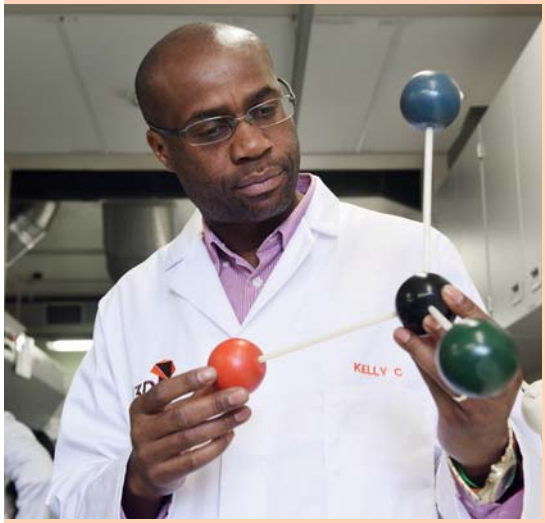
"I think the next 'big thing' for the small molecules field is how our industry will continue to strive towards more solutions and getting treatments to patients faster. Undoubtedly, we have made great strides in this, but the incorporation of new technologies and fully-integrated outsourcing, from discovery to commercial production, will drastically reduce timelines. This could make the difference between a healthcare product's success or its failure. We must continue to help innovators improve both rates of productivity and attrition – that's where I see the next big revolution occurring, and contract manufacturers have a central role to play."

### THOMAS CECH

DISTINGUISHED PROFESSOR AT UNIVERSITY OF COLORADO, BOULDER

In 1989, Thomas won the Nobel Prize in Chemistry along with his colleague, Sidney Altman, for their discovery of the catalytic properties of RNA. Thomas is currently an Investigator with the Howard Hughes Medical Institute, and also a Distinguished Professor at the University of Colorado and Director of the university's BioFrontiers Institute. His lab discovered an enzyme, TERT (telomerase reverse transcriptase), which is part of the process of restoring telomeres after they are shortened during cell division.





### KELLY CHIBALE

NEVILLE ISDELL CHAIR IN AFRICAN-CENTRIC DRUG DISCOVERY & DEVELOPMENT AND SOUTH AFRICA RESEARCH CHAIR IN DRUG DISCOVERY AT H3D, DRUG DISCOVERY AND DEVELOPMENT CENTRE AT THE UNIVERSITY OF CAPE TOWN

As director and founder of H3D, a research and development project at the University of Cape Town, Chibale is dedicated to dispelling afro pessimism – the idea that Africa has nothing to contribute to the global economy. Chibale's research focuses on delivering treatment options for tuberculosis and malaria that are both safe and affordable.

"I believe polypharmacology will go a long way to address and delay the emergence of drug resistance arising from mutations in a single target. It will also have the added advantage of benefiting patients by minimizing the pill burden and cost associated with combination drug regimens which currently require two or more small molecules that inhibit different single targets to be combined."

## PAOLO COLOMBO

EMERITUS PROFESSOR AT THE UNIVERSITY OF PARMA

Paolo Colombo joined the University of Parma in 1986. His strong interest in drug delivery research, particularly oral, transdermal and inhalation delivery, have led him to patent over 40 different drug delivery systems, many of which have become registered products. Colombo is also on the editorial board of several pharmaceutical publications and is a member of the American Association of Pharmaceutical Scientists

## EDWARD HAEGGSTRÖM

CHIEF EXECUTIVE OFFICER AT NANOFORM

In 2015, Edward Haeggström commercialized the nanoparticle engineering platform he developed with Jouko Yliruusi, Acting Professor at the University of Helsinki, with the launch of Nanoform. The company offers API particle-size reduction services and won the CPhI Award for Formulation in 2019. Haeggström is also a professor at Helsinki University and Head of the Electronics Research Laboratory within the Department of Physics. "I have always been inspired by Frederick Sanger and John Bardeen. They are the only people who have won a Nobel Prize in the same category twice – Frederick Sanger for Chemistry and John Bardeen for Physics," he says.

## JOHN CHIMINSKI

CHAIR AND CHIEF EXECUTIVE OFFICER AT CATALENT PHARMA SOLUTIONS

"Despite the rise in biologic-based medicines, we cannot forget the vital role that small molecule drugs continue to play in the treatment of so many conditions. These drugs, however, are now often more complex than ever and bring new challenges to drug developers and formulators, especially in the areas of bioavailability, differentiation and patient centricity. The future lies in finding new ways to formulate and deliver complex molecules, and in designing dose forms that are effective and that foster patient acceptance."

## JOHANNES KHINAST

PROFESSOR OF PHARMACEUTICAL ENGINEERING AT GRAZ UNIVERSITY OF TECHNOLOGY

Johannes Khinast has worked with numerous pharmaceutical companies as an advisor for the implementation of novel drug formulations. As the scientific director of the Research Center Pharmaceutical Engineering, Graz, Austria, he works with multidisciplinary teams to develop advanced medicines and continuous processes. His interests in pharmaceutical engineering and chiral catalysis have led him to patent several products related to pharmaceutical manufacturing.

## ALISON HOLMES

PROFESSOR OF INFECTIOUS DISEASES AT IMPERIAL COLLEGE LONDON

Alison Holmes' long-standing interest in antimicrobial resistance has been a driving force in her career. She is also a Fellow of the Academy of Medical Sciences and an NIHR Senior Investigator. Holmes leads a multidisciplinary research group and collaborates with international organizations to help improve the pharmaceutical industry's response to antibiotic-resistant infections.

## STEVEN M. KLOSK

PRESIDENT AND CHIEF EXECUTIVE OFFICER AT CAMBREX CORPORATION

"I believe that the next big thing for small molecules is actually an old thing, and that is the speed that clinical candidates can progress through the development process, and specifically the acceleration of the speed from IND to NDA. This touches areas of process improvements such as the use of quality by design, as well as the use of different technological concepts. One such method is the use of continuous flow chemistry where applicable in the process, and Cambrex is working with customers to use this technology for general chemistry processing to exploit the advantages it offers."

## NIGEL LANGLEY

GLOBAL TECHNOLOGY DIRECTOR, PHARMA SOLUTIONS AT BASF CORPORATION

"COVID-19 has certainly changed the world and has sadly shown how vulnerable we all are without an effective treatment for this infectious disease. I am truly impressed by the commitment and collaboration that is occurring within the pharmaceutical industry to help tackle this disease both by investigating the repurposing of existing drugs as well as accelerating a new effective vaccine. There is a common target that the whole industry is working on , one where collaboration is center stage."

## DUJUAN LU

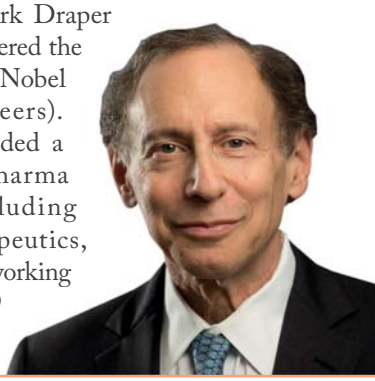
E&L MANAGER/GLOBAL LEADER AT SGS LIFE SCIENCES

"Although biological drugs have been rising stars in the industry, small molecule drugs remain essential for the majority of treatments for patients around the world. For example, most antiviral drugs are small molecules, including remdesivir, the novel antiviral drug that has shown promise in treating COVID-19 patients. The majority of new drug application approvals by FDA are still for small molecules. There are also tremendous amounts of ANDA approvals for generic drugs, which are mainly for common small molecule medicines rather than biosimilars."

## ROBERT LANGER

DAVID H. KOCH INSTITUTE PROFESSOR AT MIT

The most cited engineer in history and one of the most prolific inventors in all of medicine, Langer has nearly 1,300 issued and pending patents, many of which have been licensed or sublicensed to over 350 pharma, chemical, biotech and medical device companies. He has been honored with over 200 major scientific awards, including the United States National Medal of Science, and the 2002 Charles Stark Draper Prize (often considered the equivalent of the Nobel Prize for engineers). He has also founded a number of biopharma companies, including Moderna Therapeutics, which is currently working on a COVID-19 vaccine.



## FAITH OSIER

PRINCIPAL INVESTIGATOR AT KEMRI-WELLCOME TRUST RESEARCH PROGRAM; AND PROFESSOR OF MALARIA IMMUNOLOGY AT UNIVERSITY OF OXFORD

For her research into the mechanisms of immunity against Plasmodium falciparum, Osier has won multiple awards. As a trained physician, Osier has specialized in pediatrics in both Kenya and the UK. In 2014, she was awarded the Young African Scientist Award by EVIMalaR, and won the Merle A Sande Health Leadership Award and the Royal Society Pfizer Award.

## MARTYN POLIAKOFF

RESEARCH PROFESSOR OF CHEMISTRY AT THE UNIVERSITY OF NOTTINGHAM

Martyn Poliakoff is a chemist whose work focuses on fundamental chemistry and the development of environmentally friendly processes and materials. Throughout his career, he has received several accolades including a CBE in 2008. In 2019, he won the James T. Grady-James H. Stack Award for Interpreting Chemistry for the Public by the American Chemical Society. Poliakoff has also held senior positions within many organizations dedicated to chemical research. He was named both Foreign Secretary and Vice-President of the Royal Society in 2011, and held the position for five years. He was also appointed Honorary Professor at Beijing University of Chemical Technology in 2018.

## G.V. PRASAD

CO-CHAIR AND MANAGING DIRECTOR AT DR REDDY'S

After becoming CEO in 1990, Prasad led the global expansion of Dr Reddy's, especially in developed markets. He is also passionate about sustainable manufacturing and business practices. He leads the company's sustainability initiatives including the adoption of green technologies and processes. He was a Regional Honoree for the 2020 YPO Global Impact Award, received the V. Krishnamurthy Award for Excellence by the Centre for Organizational Development in 2019, and was designated The Boundary Breaker at the CEO Awards in 2018.

## NIKLAS SANDLER

CHIEF TECHNOLOGY OFFICER AT NANOFORM

Niklas Sandler has extensive experience in both industry and academia, particularly within the fields of pharmaceutical product development and material science. Alongside his role as chief technology officer at Nanoform, he is also a professor at Åbo Akademi University, with over 100 published papers in several pharmaceutical journals. He has a strong interest in the ways that small molecules can be used to bolster new technologies.

"Small molecules are still a crucial part of development pipelines and cover many therapeutic areas. New technologies, including nanotechnology, will boost the potential of these molecules to create future therapies. Also, old treatments will benefit from technologies that improve drug performance and provide life cycle extension opportunities for existing drugs."

## MATTHEW TODD

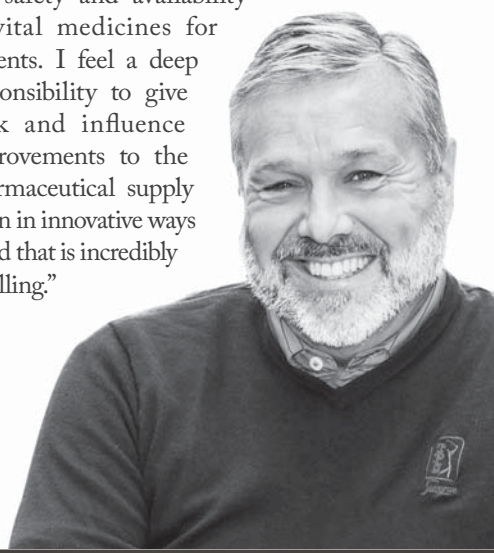
CHAIR OF DRUG DISCOVERY AT UNIVERSITY COLLEGE LONDON

Todd founded and leads the Open Source Malaria and Open Source Mycetoma consortia, which focus on the ways open science can be used to accelerate research. His research interests include the development of new ways to make molecules, particularly how to make chiral molecules with new catalysts. He is also on the editorial boards of several publications including Nature Scientific Reports and PLoS One.

## MARTIN VAN TRIESTE

PRESIDENT AND CHIEF EXECUTIVE OFFICER AT CIVICA RX

Martin Van Trieste is the president of Civica Rx, a company founded in 2018 in response to drug shortages and high prices. Prior to setting up the company, he held positions in the Parenteral Drug Association and was a special advisor to FDAzilla. "From a professional perspective, I recognize now more than ever the importance of using my experience and expertise to help improve the safety and availability of vital medicines for patients. I feel a deep responsibility to give back and influence improvements to the pharmaceutical supply chain in innovative ways – and that is incredibly fulfilling."



## JOYL SILVA

GENERAL MANAGER AT PFIZER CENTREONE

"I am excited to deliver on the innovative promise that small molecules are expected to bring to key therapeutic areas. The growth of highly potent APIs and the combined use of small molecules with ADCs represents an exciting opportunity for pharma and gives patients hope. Given the evolving potency and complexity, the life science sector will continue to demand that we work alongside other areas of industry to deliver new specialized technologies so that targeted precision medicine is available when patients need it most."

Pfizer CentreOne

Wait a minute. What? Pfizer offers API supply and CDMO services?

Yes, we do. Collaborate with Pfizer CentreOne. And access our manufacturing network for your API and finished dosage form needs.

## Welcome to Pfizer CentreOne®. We're a global CDMO embedded within Pfizer and a leading supplier of specialty APIs.

Backed by Pfizer resources, we deliver technical expertise, global regulatory support and long-term supply. For more than 40 years, we've been guiding complex compounds securely and efficiently from development through commercial manufacture.

### Listening. Solving. Guiding.

Working together with our customers, we combine our knowledge with open dialogue to solve challenges.

### Intelligent collaboration with Pfizer CentreOne.

### APIs & Intermediates

Pfizer CentreOne has been a leading provider of specialty APIs. You can count on us to deliver you a high-quality molecule over the long term.

### Custom API

Pfizer CentreOne specializes in small-molecule API synthesis. We can perform almost any kind of chemistry you need.

### Oral Solids

Pfizer CentreOne excels in the manufacture of oral solid dosage forms.

### Sterile Injectables

Pfizer CentreOne is a global leader in sterile injectables fill-finish.

## Let's collaborate

www.pfizercentreone.com


# BIOSTAT STR® Generation 3 and BIOBRAIN

## Engineered for Ultimate Upstream Performance

Simplifying Progress

The BIOSTAT STR® single-use bioreactor system is designed for rapid process development and seamless scaling to commercial manufacturing. It is powered by the new BIOBRAIN automation platform and BioPAT® analytical tools to deliver outstanding speed, quality, and productivity.

**For more information, please visit sartorius.com/biostat-str**

SARTORIUS

# NextGen

*R&D pipeline*
*New technology*
*Future trends*

# Fast-Farming Pharma

## How plants could speed up vaccine manufacture to tackle the COVID-19 pandemic

At the start of April 2020, the global number of confirmed COVID-19 cases was rapidly approaching 1.5 million; the death toll: over 80,000. And these numbers will likely have changed substantially since the publication of this article. A vaccine is urgently needed. Pharma companies are scrambling into action with vaccine candidates and early trials, but drug development will take time. Some companies, however, are taking a different approach by introducing technologies that could help with research or manufacturing. As just one example, iBio is hoping its technology can help accelerate manufacturing and scale up for a potential vaccine. The company is developing a new vaccine for COVID-19 and has partnered with Beijing CC-Pharming to test the vaccine in China. The vaccine will be produced using iBio's FastPharming system – a manufacturing technology that uses plants for rapid scale-up. We speak with Robert Erwin (President) and Sylvain Marcel (Vice President of Protein Expression Sciences) from iBio to find out more.

What are the challenges when it comes to developing a vaccine for a new virus, such as SARS-CoV-2?

There are challenges to developing any safe and effective vaccine, but even more so once an outbreak has already begun. First, a scientific team must determine which and how many targets to focus on to create vaccine candidates that will produce a protective immune response. Just producing an immune response is relatively easy, but producing an immune response that is protective and durable is not. In addition, the vaccine candidate must not produce a harmful immune response that might cause unwanted side-effects, or potentially even make a person more susceptible to viral infection – an effect referred to as "antibody-dependent enhancement." This was a serious problem in past attempts to develop a safe and effective vaccine against Dengue fever.

We felt a responsibility to take a proactive role in the response to SARS-CoV-2, especially as our FastPharming facility was purpose-built for just this kind of scenario. We've made our advanced manufacturing systems available as a CDMO, while at the same time developing our own proprietary vaccine candidates.

Not every company has the appropriate enabling technologies and capabilities, but there are definitely roles for big pharma companies to play in this response. This can be by directly supporting the efforts of companies pursuing vaccines and therapeutics for SARS-CoV-2, or simply ensuring that there are no critical interruptions in the supply chains of any necessary medicines.

*"Just producing an immune response is relatively easy, but producing an immune response that is protective and durable is not."*

One thing that this pandemic has absolutely made clear, however, is that there is a crucial need for governments to proactively provide funding to ensure that we develop robust, sustainable response capabilities so that we are collectively better prepared to respond to future pandemics.

Why must research teams consider manufacturability even at the early stages of development?

A vaccine must be administered to large numbers of people at a reasonable cost to be effective in preventing disease spread within populations. To be practical, the vaccine must be priced affordably and obviously produced in large quantities. Any inefficiencies in the manufacturing process – or stability and storage problems with the vaccine – will extend the time required for production and raise the cost. An excellent vaccine design that cannot be turned into high-quality, finished pharmaceutical


iBio
EMERGENCY
EXIT ONLY
EXIT


iBio

product at a reasonable cost is not worth much in practical terms. In addition, scalability and ready access to large scale production is critical, as the time required to build a production facility that meets regulatory compliance for a vaccine takes years.

What's the story behind the FastPharming facility? And how did the Defense Advanced Research Projects Agency (DARPA) get involved?

iBio's FastPharming facility was originally constructed in 2010 with funding from the Defense Advanced Research Projects Agency (DARPA), part of the US Department of Defense, which was exploring a range of technologies that could enable faster responses to outbreaks. Plant-based expression technology won out, and the facility was one of three commercial sites comprising the "Blue Angel" initiative.

As part of the DARPA Blue Angel H1N1 program, the facility was designed and built to manufacture kilogram quantities of recombinant proteins within months versus the historically longer time frames needed for more traditional systems. Its rapid launch to production has been designed specifically for medical countermeasure responses.

*"During a pandemic, having the ability to rapidly scale up, with confidence, is invaluable."*

Today, iBio's site in Bryan/College Station, Texas, is among the largest cGMP-compliant biotherapeutic production facilities in the world for the production of recombinant protein in N. benthamiana, with a capacity to produce bulk clinical protein at the scale of 0.5–1 kg per month, or 15–30 million doses/month (at 30 µg/dose). The site is equipped with automated hydroponics and vertical farming systems for the production of a wide array of biological medicines.

Why did you choose to focus on plant-based production?

Unlike traditional cell-culture bioprocesses that are performed in stainless-steel or single-use bioreactors, the FastPharming system uses plants as bioreactors. The gene or genes encoding the protein or proteins of interest are temporarily transfected into the leaves of hydroponically-grown plants. Pharmaceutical proteins accumulate in the leaves as the plants grow over a period of 4 to 7 days, and the leaves are then harvested. The protein is isolated, purified, and formulated into the desired drug or vaccine product. The plant we use is a relative of the tobacco plant.

Plant-based production saves months in initial setup time compared with traditional pharma manufacturing methods, and there is no need for expensive, labor-intensive, cell-line development. The risks and delays associated with manufacturing scale-up are also reduced – it's easy to grow more plants. In addition, the protein for pharmaceutical use obtained during the research stage is highly comparable to the protein obtained at the commercial scale. During a pandemic, having the ability to rapidly scale, with confidence, is invaluable.

How and why did you partner with Beijing CC-Pharming?

We began working with CC-Pharming back in 2018, with an initial focus on an anticancer antibody and the design of processes and facilities for manufacturing in China. The original agreement was written in the expectation that iBio and CC-Pharming would eventually select additional product candidates for joint development and commercialization. When it became clear in mid-to-late January that the new coronavirus was going to be a problem, the companies agreed to work together to design, produce and test vaccine candidates. We plan to have CC-Pharming test our proprietary vaccine candidates in China. We will soon enter the in vivo testing phase with one or more candidates, and expect further evaluation and development to occur in both the US and in China.

SPECIAL SERIES
*Advanced Medicine*

# Advanced Medicine: Replicating the mAb Success Story

**What lessons has the industry learned from the manufacture of monoclonal antibodies? And how can these help us face the challenges presented by viral vector production for cell and gene therapies?**

The rise of monoclonal antibodies (and other important biopharmaceuticals) has taught the industry much in terms of how to successfully manipulate and manufacture living cells to achieve the desired yields and properties. But the next stage of evolution for drug manufacturers is far more complicated and tends to require the production of viral vectors. Relatively few cell and gene therapies have been commercialized so far – and prices are high, reflecting the increased development and manufacturing challenges. There is a long way to go before the industry can say it has truly optimized the processes for bringing these advanced therapies to market. Clive Glover, Director, Cell and Gene Therapy, and Rene Gantier, Director Biotech Process Research & Development, both from Pall, review the progress so far and assess how manufacturing can be improved for viral vectors.

What cell and gene therapy milestones have we passed in recent years?

*Clive Glover:* Well, there have been exciting approvals and some amazing results coming from the clinic. One key milestone that stands out to me in particular, is the deal signed between Novartis and the University of Pennsylvania in 2013 because it really kicked off the CAR-T field and put advanced medicine in the spotlight for big pharma and investors. And then we saw the beginnings of companies like Kite Pharma, which was purchased by Gilead, and Juno Therapeutics, later purchased by Celgene. When it comes to the gene therapy side, there are many small gene therapy companies that have been struggling along for years, but 2013 saw investors really stand up and take notice of these, too. Today, there is a phenomenal amount of investment going into both cell therapy manufacturing and gene therapy manufacturing. According to estimates, around $22 billion in capital funding was committed to the industry in 2018, which is a 30 percent increase on the funding received in 2017.

*Rene Gantier:* This is a big moment for the sector, especially for gene therapy, which has been waiting a long time. The money pouring into the field means that companies can start to tackle the challenges associated with industrialization and figure out how we safely bring these therapies to as many patients as possible.

The gene therapy sector has suffered from hype in the past. What's different now?

*Glover:* Safety issues almost killed the gene therapy industry in the early 2000s, but what has changed since then is the safety profile of the viruses being used. For gene-modified cell therapies, the next generation of lentiviral vectors being used today have a high safety profile. Many patients have recently been treated with CAR-T therapy and we haven't seen issues with insertional mutagenesis, which was a problem with earlier generations of gene therapy. Over on the viral gene therapy side of things, there has also been a recent switch away from adenovirus to adeno-associated virus, which has much lower immunogenicity and a higher safety profile.

*Gantier:* We also know much more about the science behind these therapies. When you compare what is going on in the gene therapy field to what we've seen in the past for monoclonal antibodies (mAbs), there are

obvious parallels. The early days for mAbs were a little shaky, but as science in the area improved, so too did safety. We now know how to modify genes to obtain different proteins of interest with the correct mutation, and how to humanize the mAbs to reduce the risk of immunotoxicity and immunogenicity. The industry succeeded in overcoming the challenges for mAbs so there is no reason why we cannot do the same for gene therapies.

Cell and gene therapies are often grouped together under "advanced medicines", but how do manufacturing and scale up approaches differ between the two?

*Glover:* For mAbs, the manufacturing process is a fairly uniform process. In contrast, the significant number of extra steps and workflows that can be used for cell and gene therapies add complexity. The two most common workflows for advanced medicines are viral vectors and CAR-T.

At a very high level, the viral vector workflow bears a resemblance to the mAb workflow, as a single batch can serve many patients. To make more viral vectors and serve more patients, you need to scale up your process, which can become less complex and less expensive as a result. A lot of the unit operations, at a high level, look similar to the mAb process, but when you get into the detail of those operations, they are very different. When it comes to cell processing, the manufacture of CAR-T therapies is autologous; one batch equals one patient. If you want to make more therapies, you need to scale out and increase the number of batches without increasing the risk of mix up or cross contamination – and that makes manufacturing complicated. And expensive.

*Gantier:* The workflows for cell and gene therapies are different, but one thing in common for gene therapies and many cell therapies is the need for viral vectors. Producing and purifying viral vectors is challenging and has proven to be a major bottleneck for manufacturers. The industry can adapt and customize some standard bioprocessing techniques for viral vectors, but we also need new approaches. Patients can't wait so borrowing tools from traditional biopharma manufacturing is okay for now, but it's not going to see the industry through to cost effective, optimized industrialization.

What are the biggest manufacturing challenges for viral vectors?

*Gantier:* Many of the manufacturing processes for cell or gene therapies are developed in hospitals and academic labs. Not only are they produced under non-GMP conditions, but they also require additional work and optimization to be sustainable on a commercial scale. One of the key challenges is being able to move from a scale-out approach to a scale-up approach. The technique used so far, mostly on the upstream side or the cell culture side where the virus is produced, relies on scale out. But multiplying the number of cell culture devices to increase the volume of manufacturing takes up a large manufacturing footprint and contributes to costs. However, bioreactors optimized for viral vector production have now become available, allowing companies to scale up rather than scale out.

Downstream, ultra-centrifugation is probably the best way to obtain the purest virus, but it is not a scalable process that can

be implemented in a GMP, industrialized environment. There has been a great deal of discussion in the industry about chromatography-type techniques for viral vectors – an enormous topic unto itself. I think everybody is very much aligned in terms of implementing chromatography techniques, but how we go about this is another question. For example, protein A is the chromatography workhorse for mAbs but will never be suitable for viral vectors. Companies are now exploring alternative ligands.

How can companies ensure therapies are as cost effective as possible?

*Gantier:* There are many factors that contribute to high drug costs. Technology companies can certainly help in reducing the cost of manufacturing by developing new technologies that optimize the process as much as possible and deliver high yields. We don't know exactly what percentage of a therapy's price tag is attributed to manufacturing, but it will be higher than mAbs. We do know that producing a 200-L batch of viral vectors (based on a 200-L bioreactor) costs several hundreds of thousands of dollars – and the resulting batch will most likely yield less than 10 doses for an indication like Duchenne muscular dystrophy.

*Glover:* Process development is key. Companies need to evaluate new technologies – and keep an eye on emerging approaches – and then optimize their processes and equipment. Cell and gene therapies are moving fast and benefitting from reduced approval times and specialized clinical studies, but this also means you have less time for process development. For mAbs, it takes around 8.5 years to go from preclinical to commercialization. For gene therapies, it's around 6.5 years. Given the added complexity of these therapies, we have something of a conundrum when it comes to finding the time for process development.

What recent technology (or upcoming technology) are you excited about?

*Glover:* My answer is going to sound rather self-serving, but I'm really proud of our iCELLis bioreactor, which was used to commercialize Novartis' Zolgensma gene therapy for spinal muscular atrophy. The therapy requires a fairly high dose of virus per patient and we worked closely with the developers of the therapy so that this could be achieved. The developers even told us that, without this bioreactor, it wouldn't have been possible to commercialize the therapy quickly. It emphasizes how important technological innovation is in ensuring that these advanced medicines can be brought to patients.

*Gantier:* Continuous bioprocessing is being explored for mAbs – and, in time, the great deal of effort going into development could pass onto viral vector manufacturing. Viruses are very fragile and it's very difficult to recover the active virus at the end of the process. The process also takes a long time. Intensification via a continuous process could reduce process times and improve recovery rates, allowing the industry to significantly increase the number of doses that can be made and supplied to patients.

What big changes would boost the production of cell and gene therapies?

*Glover:* For me, it's analytics. We already have a good starting point in the cell and gene therapy field with the increasing science and innovations in manufacturing technologies, but what is holding us back is the poor quality of analytics associated with viral vectors. If you are trying to optimize a process and improve yields by 20 to 30 percent, but the error bar associated with the analytical assay you are using is plus or minus 50 percent, then you have a problem. And these numbers are fairly usual in this particular industry right now.

In addition to very large error bars, there are also long turnaround times associated with many of the most well-used assays – in some cases up to two weeks. If you are trying to optimize a particular manufacturing process when your assay has such a long turnaround time, it complicates and slows down the whole process. There are industry groups and experts working to improve the quality and accuracy of analytics, and when we start to see progress, I think we'll see a real acceleration in improving manufacturing processes.

*Gantier:* Another big change on the processing side would be the ability to produce viral vectors without relying on a transfection process. Right now, the process is cumbersome, and the science is not completely controlled. We rely on plasmid DNA to go into the cell to produce the virus. Imagine modified or engineered cells that could produce viruses by themselves without any external manipulation... Going back to the mAb story, the creation of cell lines made an enormous difference to the industry and the amounts of drugs that could be produced. Imagine what we could achieve if we could do the same for viral vector manufacturing.

*"Companies need to evaluate new technologies – and keep an eye on emerging approaches – and then optimize their processes and equipment."*

ARE YOU LOOKING FOR EXPERTS IN

# MICROBIAL PRODUCTION?

## CONTRACT DEVELOPMENT AND MANUFACTURING OF BIOPHARMACEUTICALS

Richter-Helm is a Germany-based GMP manufacturer specialized in products derived from bacteria and yeasts, with a proven 30-year track record.

Count on us to flexibly provide a comprehensive range of services and customized solutions. Clients worldwide have already benefited from our commitment to good manufacturing practice and total transparency. Our work focuses on recombinant proteins, plasmid DNA, antibody fragments, and vaccines.

Richter-Helm consistently works to the highest standards of pharmaceutical quality.

**Contact us**
**+49 40 55290-436**
**www.richter-helm.eu**

RICHTER-HELM

# The Bumpy Road to a Cytomegalovirus Vaccine

**The development of a cytomegalovirus vaccine has been 50 years in the making. Are there any technologies in the pipeline that could prompt a breakthrough?**

*By Andy Lane*

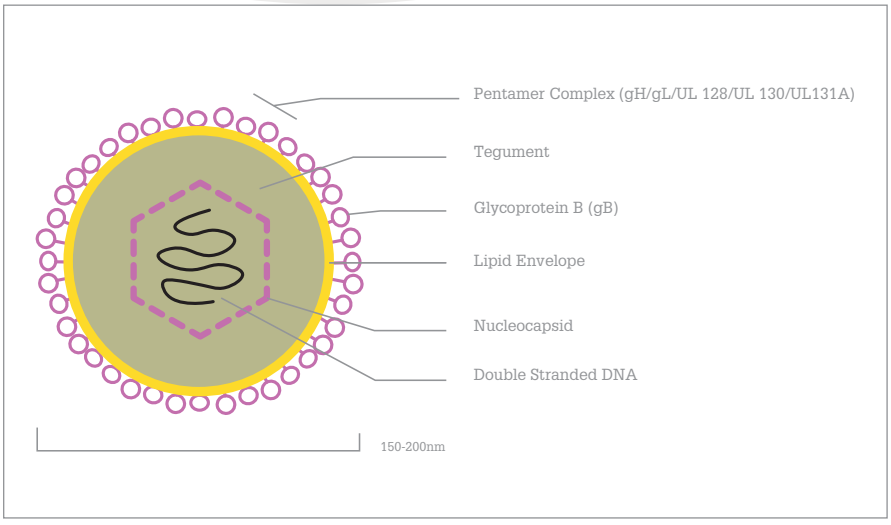



Figure 1. A diagram of a cytomegalovirus virion, with key proteins labelled.

To say that cytomegalovirus (CMV) is common would be an understatement. The virus, which belongs to the Herpesviridae family, infects the majority of people over the course of their lifetime, making it one of the most ubiquitous human pathogens in the world (1, 2). And yet general awareness of CMV and its impact on human health (particularly the risk of congenital infection) is relatively poor.

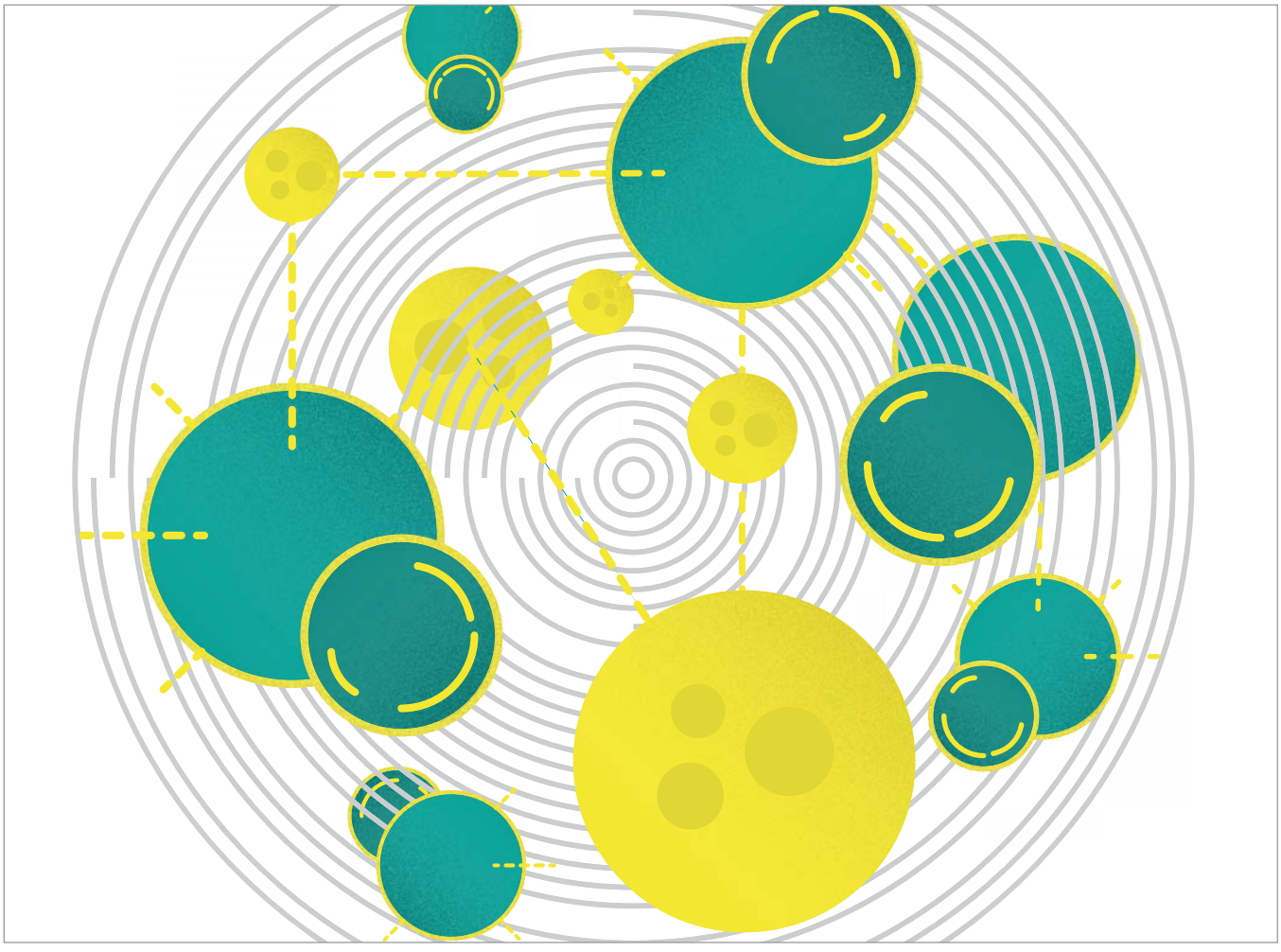
CMV has one of the largest viral genomes known to man and is composed of hundreds of proteins (see Figure 1). It exists as a variety of interrelated strains, both within the environment and those it infects (3).

Though we don't yet have a full picture of how CMV is transmitted, the virus appears to spread via a range of human bodily fluids, including urine, saliva, blood and tears. Once inside the body, it invades a remarkably broad range of cell types to mold cellular functions that support its replication. Fortunately, the immune system typically responds quickly, and drives the virus into a latent state, where it remains dormant throughout a person's life and waits for more favorable conditions (4). Given the body's natural ability to respond quickly to infection, the majority of those infected with CMV are asymptomatic, though some may present with mild symptoms, including fever, sore throat and fatigue.

## The case for a CMV vaccine

Though the majority of CMV infections are often benign and of little concern, the virus poses a significant risk to those who struggle to mount an effective immune response – a problem that occurs predominantly in two groups:

- The pregnant mother and fetus. If a new or reactivated CMV infection occurs during pregnancy, the virus can be transmitted to the placenta and establish a congenital infection in the developing fetus (cCMV). Here, it can wreak havoc on an infant's developing nervous system (5), causing irreversible defects that range from hearing loss, to impaired organ growth and learning disabilities (6). The magnitude of cCMV is significant, affecting approximately double the number of children living with better-known childhood disorders, such as Down syndrome (5), and takes the top spot for infectious hearing loss in children worldwide (7).
- Recipients of donated organs and stem cell transplants. CMV is also a threat to the recipients of solid organ or hematopoietic stem cell transplants during immunosuppressive therapy. These infections can occur due to the presence of CMV in the transplanted organ, viral reactivation in the recipient's tissue, or primary infection in seronegative recipients. Transplant-acquired infections can cause conditions, such as hepatitis, pneumonia and viremia (1) – all of which increase the likelihood of transplant rejection and graft-versus-host disease. The incidence of CMV infection among transplant recipients is remarkably common, with 20–70 percent of recipients acquiring an infection in the first year post-transplant (1), making it one of the most common complications affecting the survival of transplant recipients worldwide (8).



Despite its significant burden, no effective countermeasures are currently in place to protect those at risk, with only basic screening or behavioral measures, such as hand hygiene, available (7). And while antiviral therapies have been invaluable, they are limited by toxicity and the continual emergence of viral resistance.

Much like the rubella vaccine, a novel vaccine for CMV could protect mothers and their developing infants from CMV. Similarly, a vaccine for transplant recipients would avoid the need for expensive antiviral treatments that are limited in efficacy and duration, drastically improving patient survival and procedure success rates.

*"Much like the rubella vaccine, a novel vaccine for CMV could protect mothers and their developing infants from CMV."*

No licensed vaccines are currently available, but researchers haven't been sitting idle; the development of CMV vaccines has been ongoing for nearly 50 years (9). Major impediments to the development of a suitable vaccine have likely been down to poor general awareness of the virus and its immunological complexity. However, the acknowledgement of the clinical significance of CMV in recent years has stimulated a surge in funding and research interest.

## The current pipeline

### *Attenuated vaccines*

Attenuated vaccines are created by reducing the virulence of a pathogen, while still keeping them viable. They have the potential to be one of the most effective ways of vaccinating against CMV, as they can mimic a natural infection (10). The 1990s saw the development of the first attenuated vaccines – a new generation of so-called transgenic disabled infectious single cycle (DISC) strains (see Figure 2) (11). These are live viruses with selective gene deletions in their membrane proteins that allowed them to assemble after their first infection cycle, but which were unable to infect successive cells (12). By expressing only a limited subset of the viral proteome, DISCs can be propagated under controlled conditions that allow for their production in vitro, but cannot replicate in vivo, preventing latent infection (13).

The current DISC frontrunner is Merck's V160 strain, which includes rapamycin-binding protein (RBP) insertion. In vivo, RBPs are rapidly degraded to prevent viral replication. DISC strains such as these have effectively mitigated the concerns of viral replication and latency, and could, in theory, elicit the full repertoire of antibody and T-cell responses of a natural infection. However, considering that natural CMV infections can fail to provide the immunity required to prevent a secondary infection, it remains unclear if these vaccines will offer sufficient protection. Merck's recent phase I trials have shown good tolerance (14) and a phase II study of 2,100 women, aged 16–35 is now underway, with results expected in 2021 (15).

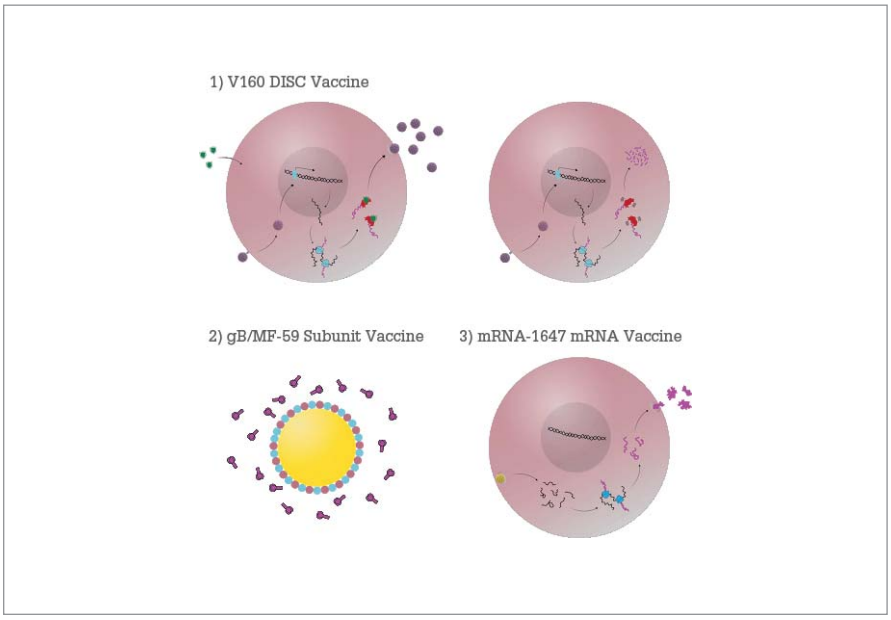



Figure 2. Diagram illustrating DISC, subunit and mRNA vaccines. 1) In vitro (left), Shield-1 ligand is added to cell culture alongside V160 formulation. This stabilizes the replication complex and allows the virus to proliferate; in vivo (right), no Shield-1 ligand is present, which causes destabilization of the replication complex and prevents viral assembly. 2) The adjuvant MF59 is comprised of squalene, surrounded by surfactants and formulated with subunit antigens. 3) A lipid nanoparticle fuses with cell membranes to release 6 mRNAs into the target cell cytoplasm. The mRNAs are translated by host cell machinery to produce antigens that can be detected by the immune system.

### *Subunit vaccines*

Subunit vaccines (see Figure 2) are created using fragments of pathogens (typically surface proteins are used for their development) and are used to trigger an immune response and stimulate acquired immunity against the pathogens from which they are derived. The protein responsible for mediating CMV's entry to human cells and the dominant target of the body's humoral response is glycoprotein B (gB) – a homotrimeric envelope protein that has seen considerable development as an antigen in subunit vaccines. Formulated with Novartis' proprietary MF59 adjuvant, gB has shown some promising early results by a range of vaccine developers and has arguably advanced the furthest to date in clinical trials (16).

In a 2007–2010 phase II trial of postpartum women, Sanofi Pasteur's gB/MF59 formulation demonstrated 50 percent efficacy against primary CMV infection in seronegative women vaccinated within one year of giving birth, with acceptable adverse events (17). This landmark study was the first to demonstrate efficacy in preventing primary CMV infection, and was followed three months later by a phase II in transplant recipients that showed significantly reduced viremia and length of antiviral therapy required (18).

A glance over the literature makes it clear that no major breakthroughs with gB subunit vaccines have taken place since. A likely reason for this was the realization that CMV's pentamer complex is also a key target for neutralizing antibodies and would be required in formulations (19). Combined with the fact that gB has reached only 50 percent efficacy, and that the immune responses to gB and pentamer stimulate protection in different cell types, it is

*"A slightly disconcerting consideration is that we still don't fully understand how protective immunity is conferred by natural infection with CMV."*

likely that an effective vaccine will need to consist of both proteins (20).

*RNA Vaccine*

A recent entrant to the CMV race is Moderna, which has been developing novel messenger RNA technologies since their founding in 2010. Unlike protein-based vaccines, Moderna's mRNA-1647 formulation uses mRNA to instruct the host's cells to produce antigens on-site, making manufacture and administration far simpler (21). The formulation comprises a lipid nanoparticle, that contains six separate mRNAs, collectively encoding five of the pentamer complex subunits and gB.

Earlier this year, Moderna released some promising phase I trial data (22). Results showed good toleration and no severe adverse events after a three-dose schedule, and boosting of neutralizing antibody titers in both seronegative and seropositive participants; 10-fold and 20–40-fold, respectively (23). Moderna are now taking their vaccine forward, making it the first mRNA vaccine for an infectious disease to enter a phase II clinical trial. Moreover, plans are already in place for a phase III in 2021, which will evaluate efficacy in up to 8,000 women of childbearing age.

Though attenuated, subunit and RNA vaccines are demonstrating varying levels of success in the clinic, there are a wide range of other vaccine strategies beyond the scope of this article, including peptide, DNA and vectored vaccines, all of which present viable options for tackling CMV.

## What next?

It's clear that the industry has made significant advances in our understanding of CMV in recent years, with a range of emerging technologies that could soon see a breakthrough. However, to develop an effective vaccine that can prevent both in utero and transplant-associated infections, some key challenges will need to be addressed.

A slightly disconcerting consideration is that we still don't fully understand how protective immunity is conferred by natural infection with CMV (13). Though this must have made vaccine design feel like a shot in the dark for researchers in the past, emerging data is now starting to paint a more detailed picture. A vaccine will need to stimulate both the humoral and cell-mediated immune responses, as anti-CMV antibodies have been shown to prevent transmission and minimize clinical manifestations, while T-cells are likely involved in suppressing viral replication and prevent reactivation of infection (2, 23). Further research is necessary to provide a clearer picture that defines the correlates of protection.

Immunization is also challenged by the fact that natural infection with CMV is only partially protective and does not prevent placental transmission of the virus (24, 25). And that means vaccine candidates will need to provide protection exceeding that of natural infection (8), and may make the prospects for traditional vaccines somewhat limited (26).

An ongoing challenge in biologic manufacturing has been the need to maintain homogenous cell lines that can be scaled to yield vaccines of a

high enough purity for use in humans. mRNA technologies, such as Moderna's, are entirely cell-free and avoid the need for complex manufacturing processes, which would make these strategies much more practical for real-world use. However, it has yet to be seen whether mRNA vaccines are able to consistently elicit potent and long-lasting immune responses to CMV.

Another serious consideration: how to practically evaluate efficacy in trials. cCMV is fairly rare at the population level (about 1 in 150 pregnancies) and occurs in mostly vulnerable patient populations. In practice, this requires large patient samples in resource-limited populations, which may deter more risk-averse developers. Likewise, determining practical endpoints can be a headache when you consider that viral transmission, prevention of maternal infection, blocking of cross-placental transmission, reduction in congenital infection in infants, transplant survivability, and reduction in antiviral treatment are all clinically relevant (27).

Despite these challenges, the industry remains optimistic. Successful phase III trials from vaccine front-runners, such as V160 and mRNA-1647, could clear the path to market in the coming years. And though the road towards a CMV vaccine has been long and bumpy, encouraging results from a wide scope of vaccine types suggests that we're getting closer to a future where CMV poses less of a risk to those most vulnerable to infection.

*Andy Lane is Commercial Director at The Native Antigen Company*

*References*


1. *X Cui, CM snapper, "Development of novel vaccines against human cytomegalovirus", Hum Vacc Immunother, 2673-2683 (2019).*
2. *SA Plotkin, SB Boppana, "Vaccination against the human cytomegalovirus," Vaccine, 37(50), 7437-7442 (2019).*
3. *A Ross et al., "Mixed Infection and Strain Diversity in Congenital Cytomegalovirus Infection", J Infect Dis, 204(7), 1003-1007 (2011).*
4. *NB Knipeet al., "Fields Virology", Wolters Kluwer Health, 1-3091 (2007).*
5. *MC Cheeran et al., "Neuropathogenesis of Congenital Cytomegalovirus Infection: Disease Mechanisms and Prospects for Intervention", Clin Microbiol Rev, 22(1), 99-126 (2009).*
6. *SC Dollard et al., "New Estimates of the Prevalence of Neurological and Sensory Sequelae and Mortality Associated With Congenital Cytomegalovirus Infection", Rev Med Virol, 17(5), 355-363 (2007).*
7. *SB Boppana et al. "Congenital Cytomegalovirus Infection: Clinical Outcome", Clin Infect Dis, 57, S178-S181 (2013).*
8. *DJ Diamondet al. "A fifty-year odyssey: Prospects for a cytomegalovirus vaccine in transplant and congenital infection", Expert Rev Vaccines, 17(10), 889-911 (2018).*
9. *SA Plotkin "The history of vaccination against cytomegalovirus", Med Microbiol Immun, 204(3), 247-254 (2015).*
10. *KY Choi et al., "A Novel Non-Replication-Competent Cytomegalovirus Capsid Mutant Vaccine Strategy Is Effective in Reducing Congenital Infection", J Virol, 90(17), 7902-7919 (2016).*
11. *DM Koelle and L Corey, "Recent Progress in Herpes Simplex Virus Immunobiology and Vaccine Research", Clin Microbiol Rev, 16(1), 96-113 (2003).*
12. *MJ Reddehase,"Cytomegaloviruses: From Molecular Pathogenesis to Intervention", Caister Academic Price, 1-464 (2013).*
13. *T M Fu et al."Progress on Pursuit of Human Cytomegalovirus Vaccines for Prevention of Congenital Infection and Disease", Vaccine, 32(22), 2525-2533 (2014).*
14. *Merck Sharp & Dohme Corp., "Safety and Immunogenicity of the Human Cytomegalovirus (CMV) Vaccine (V160) in Healthy Japanese Men (V160-003)" (2019), Available at: http://bit.ly/387J4OY*
15. *Merck Sharp & Dohme Corp., "Safety, Tolerability, and Efficacy of the Human Cytomegalovirus Vaccine (V160) in Healthy Women 16 to 35 Years of Age (V160-002)" (2019). Available at: http://bit.ly/399hItc.*
16. *TM Fu et al., "Progress on Pursuit of Human Cytomegalovirus Vaccines for Prevention of Congenital Infection and Disease", Vaccine, 32(22), 2525-2533 (2014).*
17. *NIAID, "Recombinant CMV gB Vaccine in Postpartum Women" (2011). Available at: http://bit.ly/2PvwjHR.*
18. *NIAD, "CMV Glycoprotein B Vaccine in Allograft Recipients" (2011). Available at: http://bit.ly/39eaNiI.*
19. *F Wussow et al. "Human Cytomegalovirus Vaccine Based on the Envelope gH/gL Pentamer Complex", PLoS Pathog, 10(11), (2014).*
20. *F Rieder and C Steininger, "Cytomegalovirus vaccine: phase II clinical trial results", Clin Microbiol Infect, 20(Supplement 5), 95-102 (2014).*
21. *C Zhang et al. "Advances in mRNA Vaccines for Infectious Diseases", Front Immunol, 10(594), (2019).*
22. *Moderna, "Moderna Announces Additional Positive Phase 1 Data from Cytomegalovirus (CMV) Vaccine (mRNA-1647) and First Participant Dosed in Phase 2 Study" (2020), Available at: http://bit.ly/2T7s1bK.*
23. *AW Sylwester et al. "Broadly targeted human cytomegalovirus-specific CD4+ and CD8+ T cells dominate the memory compartments of exposed subjects", J Exp Med, 202(5), 673-685, (2005).*
24. *CL Rosa and DJ Diamond "The immune response to human CMV", Future Medicine, 7(3), 279-293, (2012).*
25. *KM Bialas and SR Permar, "The March towards a Vaccine for Congenital CMV: Rationale and Models", PLoS Pathog, 12(2), (2016).*
26. *RF Pass et al. "Vaccine Prevention of Maternal Cytomegalovirus Infection", New Engl J Med, 360(12), 1191-1199, (2009).*
27. *CS Nelson et al., (2018). "A new era in cytomegalovirus vaccinology: considerations for rational design of next-generation vaccines to prevent congenital cytomegalovirus infection", NPJ Vaccines, 3(38), (2018).*

# The Glass Quality You Seek Does Exist

**Glass is an indispensable primary packaging material for pharma, but alongside the many benefits of conventional glass are disadvantages, such as breakages, delamination, and glass particulates. It doesn't have to be this way. Recent glass innovations can make a big difference.**

*By Robert Schaut, Scientific Director for Corning Pharmaceutical Technologies*

Everyday objects, such as a glass jar, a bottle or even a car window, tend to be made from an easy-to-melt glass composition that is fairly inexpensive to manufacture. As a result, the glass can have poor chemical durability – after all, you don't need high chemical durability for soda. But this "everyday" glass is not suitable for pharmaceutical use. For a pharmaceutical product, impurities from the primary packaging can cause problems – such as contamination, degradation of the APIs, or even pH shifts. Glass for pharmaceutical use must have excellent chemical durability to keep the drug product stable for as long as possible. This durability can be achieved by increasing the aluminum oxide in the glass or by keeping the silica content of the glass high.

Pharmaceutical filling lines process hundreds of vials a minute, creating glass-to-glass frictive contact that leads to scratches and breakage. It can also lead to small glass particles and cause down-time. The underlying cause of these challenges is that conventional borosilicate glass vials have a high coefficient of friction surface, increasing their predisposition to jam. In this situation the operators may have to intervene, increasing the potential for contamination (1).

Often, pharma manufacturers don't realize that these problems can be reduced or avoided. Background glass particles, for example, are considered the "norm" since they are created as vials rub against one another on the filling line. When one pharma company switched from borosilicate glass to Corning's Valor® Glass during a line trial, they assumed their particle monitoring equipment was broken because the particle counts in the filling environment dropped to such low levels. They hadn't realized it was possible to reduce particle counts so much simply by changing the glass!

There are many glass suppliers who highlight the processes used to make the glass, and how, for example, they reduce the potential for defects. In many instances, the solutions only address one problem – one solution tackles delamination, another reduces extractables and leachables, and a third might focus on machinability. In contrast, Corning's Valor Glass has been developed as a holistic glass solution that minimizes as many problems as possible – simultaneously.

To create Valor Glass, Corning's R&D team took a Quality by Design approach. They identified the root causes of problems like delamination and breakage and used materials science to optimize the glass composition. For example, the root cause of delamination was traced to the evaporation and condensation of boron from borosilicate glass during the tube-to-vial converting process. The resulting boron-free composition of Valor Glass specifically eliminates delamination and gives the glass low extractable concentrations (2). The low friction external surface keeps it inherently strong and damage resistant, moves smoothly through manufacturing lines, and can reduce peak particle counts by up to 96 percent.

## Quality advocates

The FDA has continued to raise concerns with the quality of conventional glass packaging through both advisory and other communications (3). Moreover, FDA has supported – through its Emerging Technology Program – advancement of new glass packaging technologies, like Valor Glass, with the potential to improve drug product quality. Traditionally, glass manufacturers have been seen as "just suppliers" to pharma manufacturers, with prices based on the cost of materials and manufacturing process. But there have been some negative consequences related to glass quality issues, such as drug recalls resulting from delamination, or from glass particles in the drug container. Poor filling line efficiency due to jamming vials or breakages can also add to manufacturing costs. These issues can be reduced with the right glass containers. A product like Valor Glass may cost a little more than conventional borosilicate glass, but it will improve manufacturing by resulting in fewer problems that could lead to delays, drug shortage or potential recalls – a win for both manufacturers and patients.

At Corning, solving tough customer problems is what we do. We do our best work when we have the opportunity to partner for innovation.

*References*


1. *CL Timmons et al., "Particulate Generation Mechanisms during Bulk Filling and Mitigation via New Glass Vial," PDA J Pharm Sci and Tech, 71, 379 (2017).*
2. *RA Schaut et al., "A New Glass Option for Parenteral Packaging," PDA J Pharm Sci and Tech, 68, 533 (2014).*
3. *FDA, "Summary of Recent Findings Related to Glass Delamination," (2018). Available at https://bit.ly/2UhJJtQ*

# The Forensic Troubleshooter

**Sitting Down With... Stephen Tindal,** Director, Science & Technology, Catalent Pharma Solutions, Swindon.

If you weren't a scientist, what would you be?

When I was at school, I toyed with the idea of being a comedy actor! But throughout my career, people have told me that I would have been a good teacher. I'm not sure I would personally have chosen a teaching career, but perhaps it would have chosen me if I hadn't focused on science.

I chose to study chemistry and analytical science at university. For a time, I had wanted to be a policeman, but I decided to fight crime in a different way by becoming a forensic scientist. After I graduated, however, I found that I couldn't really afford to leave home and survive on the starting salary of a forensic scientist. I'd like to believe that the forensic science industry lost out on a great scientist that day and they really should review their starting salaries…

Instead, I decided on a career in water analysis. I went to an interview in Swindon, UK. Next door, there was also a job in quality control going at RP Scherer and I ended up taking the QC job. Actually, it all turned out rather well!

And how was your first foray into the industry?

At the time, the company wanted a graduate with a fresh perspective to look at their testing laboratory and solve some of the problems they were experiencing with ageing methods. That really suited me because I liked mysteries and solving problems (hence my original forensic interest!). However, I didn't enjoy QC all that much. Ultimately, a lot of the problems went back to people, and although I made friends in high places by solving problems, I also made a few enemies on the bench. The work was also too repetitive and it wasn't the place for me. But then I had the opportunity to move into process development – where there were more mysteries to solve. The company had recently moved from one facility to another, and could not get some of the batches to run correctly despite using the same equipment.

After manufacturing, I moved to a formulation role. This gave me further opportunity to grow and learn, and over the next few years I spent less energy fixing issues, and more energy on putting in place a "right-first-time" methodology.

What are your proudest achievements?

At Catalent's Somerset site in New Jersey, we commercialized several products. It was crucial to be able to flag up potential manufacturing issues early enough for them to be fixed before validating the process – I'm proud of the part that I played in fixing any possible problems before they affected the business.

Over the last few years, I have been asked to write chapters on soft capsules for several publications, including the Encyclopedia of Pharmaceutical Technology and Aulton's Pharmaceutical Sciences, which are used to educate students and others. Aulton was the same book that I was given as a student to learn about the pharmaceutics part of my course! It was really nice to be recognized as an expert in the field and to give something back to the next generation.

You've also been involved with the US Pharmacopeia...

I was on an advisory panel. The more I thought about it, the more I realized that it was a terrific thing to get involved with. After monographs are drafted, they are released for people to comment on; if you're not paying attention, it's easy to miss the review window and then you have to live with the consequences of what was finally published.

Catalent makes more than 7,000 products, and I'd say there have been instances when we should have had a seat at the table when it came to monograph negotiations. People from smaller companies (and making significantly fewer products) were influencing monographs that affected our work. I stepped up to try and correct the imbalance – and it was a fantastic experience. If you're prepared to roll your sleeves up and get involved, you can make a difference. But you can't just think about your own company; you need to think about what is best for the industry overall.

Why is it so valuable to gain experience outside of your own company?

Two things are important in development. One of them is diversity of thought; getting as many different opinions about a project on the table as possible – and preferably at the beginning. If you come across unforeseen issues later on in a project, I believe it proves there wasn't enough diversity of thought early on.

The second is being able to define a continuous strategy to deliver projects successfully. Working outside your own company gives you both diversity of opinion and a better sense of when you have the right strategy.

Sometimes, even when people think there is a better way of doing something, no one wants to change – finding a new solution is extra work. But if you have other experiences you can draw on, you can show the benefits of the future state: "I've seen how other companies approach this problem. Let's try it this way…"

All that said, you don't necessarily need to move companies to gain diversity of thought, especially in a larger company like Catalent. My advice is to talk to people – both inside and outside your own department, unit or company. There is turnover in any company and there are always new people. Invite them for a coffee. Ask them about their job and what they did before. There is always an opportunity to share common experiences and maybe learn something new that will help you in the future.


# SOLVING BIOAVAILABILITY IS SCIENCE. DESIGNING TREATMENTS IS ART.

Successful formulations for better bioavailability are built on robust science, superior technologies and the art of drug design.

Catalent's expertise in solving thousands of solubility challenges with the broadest toolkit of formulation and delivery technologies, coupled with integrated screening, clinical manufacturing and supply, will help get your molecules into clinic faster, turning your science into reality. **Catalent, where science meets art.**

Catalent®

**US** + 1 888 SOLUTION (765-8846) **EUR** 00800 8855 6178 catalent.com/solubility 