MARCH 2020 # 63

the Medicine Maker™

Your Attention, Please

How do we measure up when it comes to tackling neglected diseases and helping the world's poorest patients?

16 – 31

Cambrex

Your molecule
Our mission

Drug substance | Drug product | Analytical services

Schedule a meeting at DCAT

While you're in New York, discover why we're **the** small molecule company with end-to-end capabilities.

Meet the experts you'll enjoy working with, March 23-26.

Valeska Taylor
QC Analyst

www.cambrex.com

Writing About What Matters

Sometimes, a topic deserves a little extra attention

The easiest (and, dare I say, laziest) way to write an editor's comment or foreword is to wax lyrical about the content within the issue's pages. We don't typically do that in The Medicine Maker because there are often bigger issues or trends that demand up-to-the-minute coverage. Moreover, as we don't convey our own personal opinions elsewhere in the magazine, the "editorial" is the one exciting chance we get to explore something we really care about.

But very occasionally, as is the case this month, the stars align and it seems entirely fitting to draw special attention to a topic – especially one that is, by definition, neglected. The development of our cover feature on neglected tropical diseases was certainly a wake-up call for me.

It is the mission of charities to constantly remind us about the needs and suffering of people in developing countries. But they have a tough job. Many of us are more than one step away from the issues. Sometimes we can become overexposed or saturated, hearing the messages so often that there is a danger we don't pay attention to it at all. In some cases, we don't really understand the nature of these oh-so-distant diseases – or why they are so debilitating to communities affected.

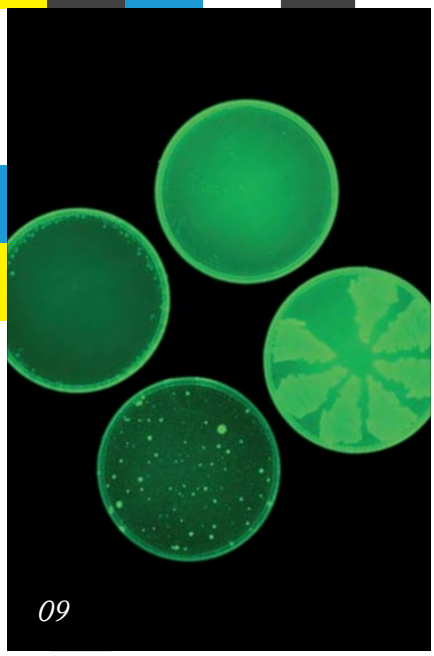
But when I am interviewing someone on the phone who tells me, in quite some detail, exactly what it was like to be amongst the people affected by river blindness or the Ebola virus, the issues suddenly become very real and far more hard-hitting. I recognized how frustrating it must be for those suffering from or trying to eradicate devastating diseases, while the rest of the world looks away. Contrast that with COVID-19 coverage.

That said, our cover feature is not (or at least is not intended to be) a harrowing experience that will make you feel guilty. Rather, the interviewees and contributors are proud of successes that should be celebrated more widely. They highlight the good that comes out of pharma companies – from donations to research to manufacturing expertise that makes new vaccines a reality. The stories are inspiring – and I hope they serve as a rallying call.

Tackling diseases that affect huge numbers of the world's poorest people can seem like a daunting challenge to put it mildly; 217.5 million people, for example, are at risk of river blindness. But, as proven on pages 16–31, it is possible to make progress – and, in some cases, a group effort can eliminate a disease altogether.

Stephanie Sutton
Editor

Contents



09

On The Cover

A health worker measures a child to administer the appropriate dose of Zithromax as part of a mass drug administration to treat trachoma near Matay in Minya, Egypt.

Image courtesy of Sightsavers/Sima Dib

Business

Profession

Sitting Down With

the Medicine Maker

ISSUE 63 - MARCH 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

Natural Evolution of NMR Methodology?

How a new approach accurately determines the structure and stereochemistry of natural products that confound conventional methods

Natural products are a common source of drugs (many antibiotics, painkillers, and even cancer drugs are derived from natural products), but before natural products can be exploited, their structures and stereochemistry must be elucidated. And that's (unsurprisingly) easier said than done.

"Besides the X-ray diffraction, which can only be applied to crystallizable molecules, chemists usually use nuclear magnetic resonance (NMR) spectroscopy for structure determination. Most employed NMR parameters rely on the measurement of protons. But for molecules that only contain few protons or flexible molecules that need more NMR data to define their conformational spaces, conventional proton-based NMR methods may not determine their structure and stereochemistry correctly," says Han Sun, a researcher at the Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP) in Germany.

Another NMR-based parameter – residual chemical shift anisotropy (RCSA) – can accurately determine structure and stereochemistry, but requires specialized instrumentation. But now, Sun and colleagues have developed a method that simplifies the measurement of RCSA to make it more accessible.

"Our experiment involves bringing together natural products with a commercially available peptide – with a sequence of AAKLVFF," says Xiaolu Li, lead author of the work (1). "Dissolved in methanol, the peptides are transformed into liquid crystals, which gives the natural products a weak orientation in the magnetic field. This particular orientation enables us to measure the RCSA of the molecules as a parameter, which in turn provides accurate information about their structure and stereochemistry."

The team tested the technique by analyzing spiroepicoccin A – which was isolated from a marine organism that lives at a depth of more than 4500 m. The substance only has a few hydrogen atoms attached to its stereocenters, making it difficult to analyze with conventional NMR, but the new technique was able to successfully elucidate the compound's structure and stereochemistry.

According to Sun, many pharma companies use residual dipolar coupling and RCSA-based methods to characterize the structure and stereochemistry of drug-like molecules – and have expressed interest in the new technique. Meanwhile, Sun, Li and their colleagues are using the new method to elucidate the structure and stereochemistry of other new marine natural products.

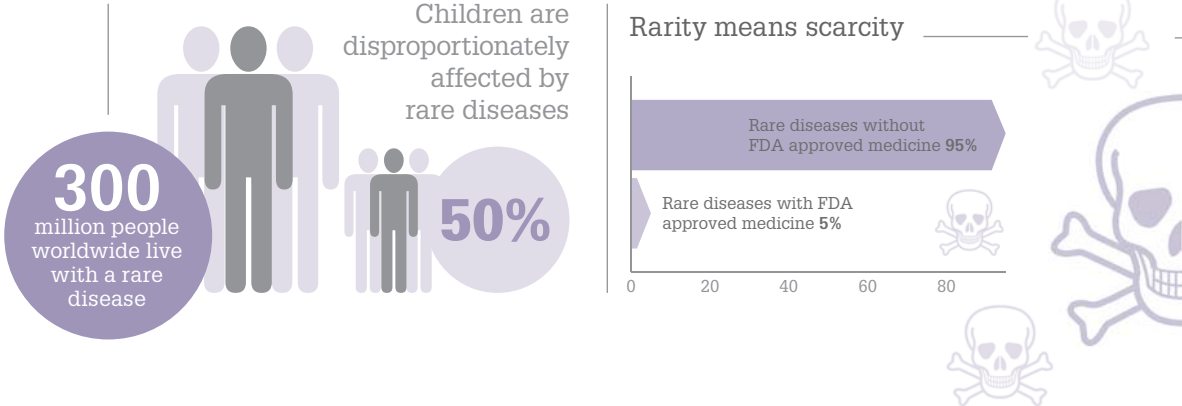
Reference

1. *L Xiao-Lu et al., J Am Chem Soc, 142, 2301-2309 (2020).*

INFOGRAPHIC

The Need to Be Seen

What is the current situation for rare diseases and orphan drug development?



BUSINESS IN BRIEF

Potential shortages, API manufacturing and coronavirus fears... What's new in business?

- The FDA has identified 20 drugs at risk of shortage due to the COVID-19 outbreak. When contacted by the agency, however, none of the manufacturers of these medicines expected to experience a stock deficit. The main ingredients of the earmarked drugs either source all main ingredients from China, or are finished in China.
- Sanofi says it is aiming to become one of the world's largest API production operations by bringing together six of its API manufacturing sites in Europe and the UK. A spokesperson for the company said that the project would help the company move away from its "heavy reliance on API sourced from the Asian region."
- The Indian government has imposed a restriction on the export of 26 pharmaceutical ingredients and drugs made in the country, as concern mounts about the potential of the coronavirus outbreak to turn into a pandemic. India sources up to 70 percent of its APIs from China. The APIs and drugs mentioned in the statement issued by Indian authorities this month account for 10 percent of drug products exported by India.

A Green Pioneer

Celebrating a career dedicated to environmental protection

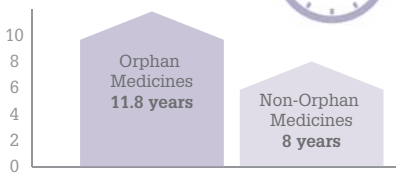
Dana Kolpin, Research Hydrologist at the US Geological Survey Central Midwest Water Science Center, Iowa, has been named the recipient of Recipharm's 2019 International Environmental Award. Kolpin has published over 220 papers and reports on environmental contaminants that are used in today's society, including pharmaceuticals. Kolpin also regularly collaborates with international colleagues to conduct research on environmental contaminants and is one of the founding organizers of Emerging Contaminants – an international conference series.

"Kolpin's work represents a pioneering approach to exploring the potential effects and risks of contaminants, including pharmaceuticals, on the environment. His research has been both influential and inspirational for other scientists in this field and has without a doubt been essential in building a stronger understanding of the environmental impact of various types of contaminants," said Lars Backsell, Chairman of the Board of Recipharm.

85% to 90%

of rare diseases are considered "seriously life threatening"

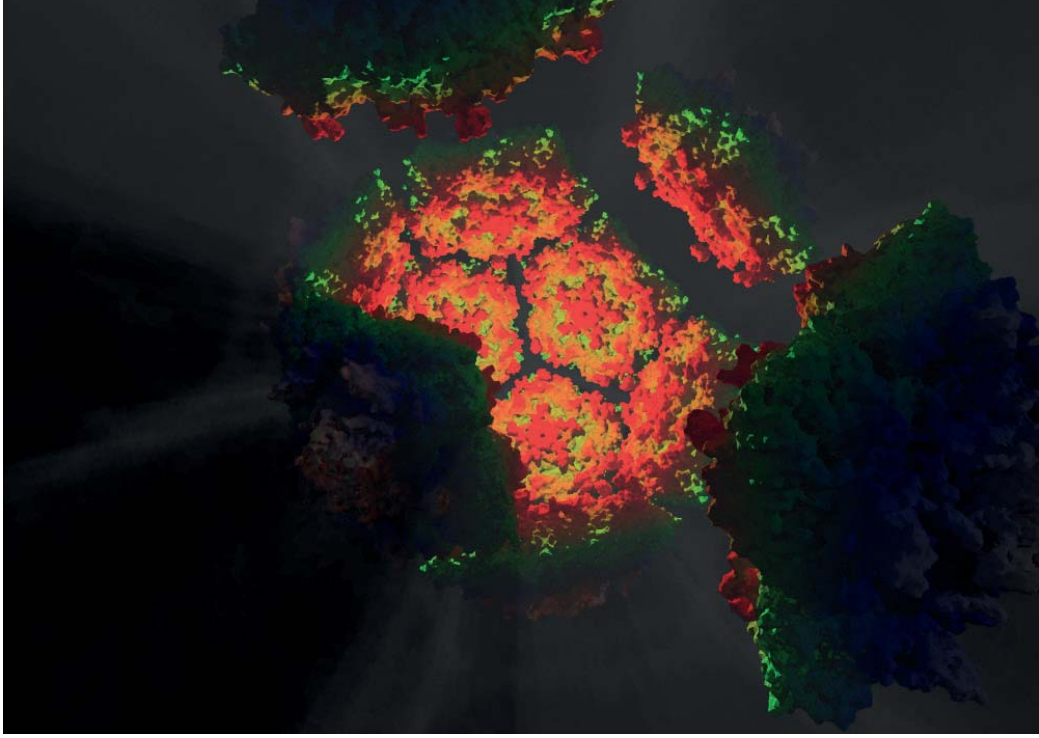
A waiting game



FDA's overall development duration

The success rate of clinical trials for orphan diseases is only **6%**

Source
PhRMA, "Rare Diseases and the Orphan Drug Act." 2019. Available at: https://onphr.ma/2TpdarX



Total Eradication

Will a new VLP-based polio vaccine help rid the world of the disease once and for all?

CPI – a member of the UK government's High Value Manufacturing Catapult – is collaborating with the University of Leeds, UK, to develop a low-cost, scalable manufacturing process for a non-infectious, stable vaccine against polio. Developed using virus-like particles (VLP), the vaccine is intended to improve the safety and accessibility of treatment, particularly in low- and middle-income countries.

Since the introduction of the Global Polio Eradication Initiative in 1988, cases of polio have plummeted by 99 percent – with the oral polio vaccine (OPV) playing a key role in facilitating large-scale immunization. But despite success with OPV, it suffers a number of drawbacks; firstly, the RNA-dependent RNA polymerase enzyme that is responsible for making copies of the PV genomic RNA is error-prone. "In rare cases, use of the OPV can, therefore, cause disease in vaccine recipients or their close contacts. In situations of low vaccine coverage, this can lead to localized outbreaks," says Natasha Lethbridge, Project Manager, CPI.

Secondly, there is a small number of immune-deficient or immunocompromised people who are unable to clear the virus after vaccination, which means they persistently shed vaccine-derived virus for long periods of time after immunization. Such individuals represent a potential source of infection if they were to stop vaccine use.

As a result, OPV is being replaced by an inactivated polio vaccine (IPV) in much of the world – but in some regions, IPV may be too expensive.

The new VLP vaccine should be able to overcome both scientific and economic issues. Composed of empty protein shells that mimic PV sufficiently to induce an immune response, the VLP vaccine lacks the genetic material needed for infectivity, overcoming biosafety concerns. "And because the vaccine can be made under low levels of containment, it would also make the product much more affordable than the current IPV offering for low and middle-income countries," says Lethbridge.

And once scientific and economic issues have been solved? Geopolitics may present the final hurdle. "It can be extremely challenging to vaccinate in remote areas," according to Lethbridge. "And, in some instances, vaccinators have been targeted by radical groups amidst regional conflicts."

A Word of Advice...

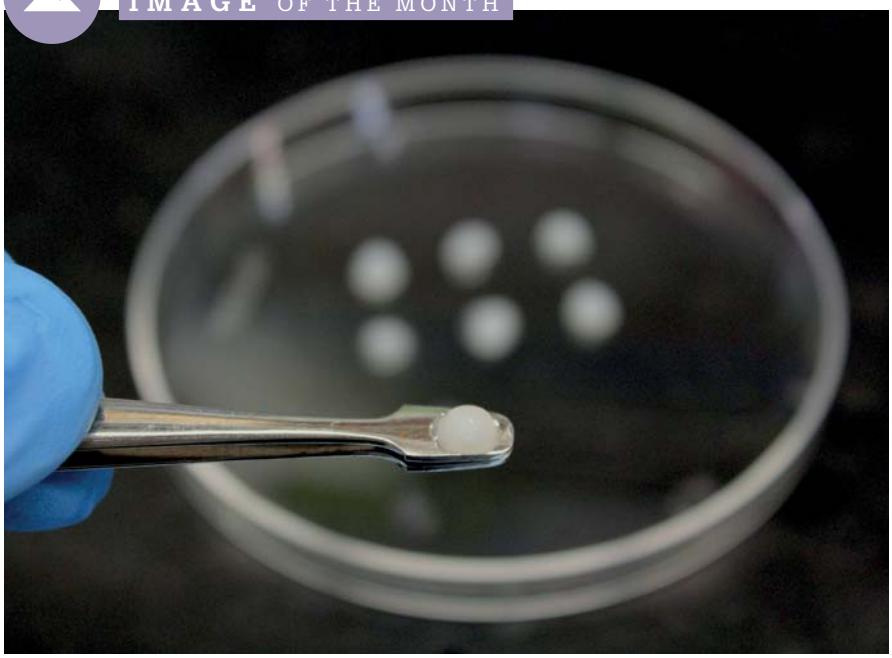
Looking to set up your own company but lacking business acumen? Help is at hand

If you're based in the UK and want to set up an oncology-based company, Start Codon and Cancer Research UK may be able to offer some advice. Start Codon, a life science accelerator, recently joined Cancer Research UK's Entrepreneurial Programs Initiative, which encourages start-ups in the oncology space.

The program provides insight into business basics, such as intellectual property laws, the fundamentals of marketing, and how to write business plans. It also aims to help applicants build a network within the industry. Applicants will have the chance to meet companies and individuals who have successfully commercialized products, giving them access to relevant and ongoing mentorship.

The partners are actively looking for companies interested in applying to the program.

IMAGE OF THE MONTH



Solid Vaccines for Liquid Tumors

Researchers at the Wyss Institute at Harvard University have developed a biomaterial-based vaccine that reportedly eliminates the deadly blood cancer, acute myeloid leukemia.

Credit: Wyss Institute at Harvard University

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

QUOTE of the month

"Critical therapies often carry a heavy price tag; the cost of insulin has risen over the past decade. Opening these products to increased competition is expected to bring down prices and help patients have access to more choices for these life-saving drugs."

Stephen M. Hahn, FDA Commissioner, on the agency's plans to increase patient access to insulin and other biologics. http://bit.ly/2I1iMDC

Antimicrobial AI

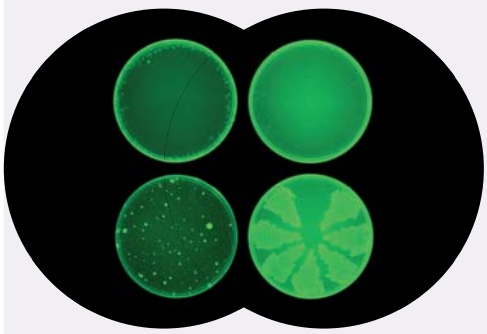
A deep-learning algorithm has identified a new antibiotic

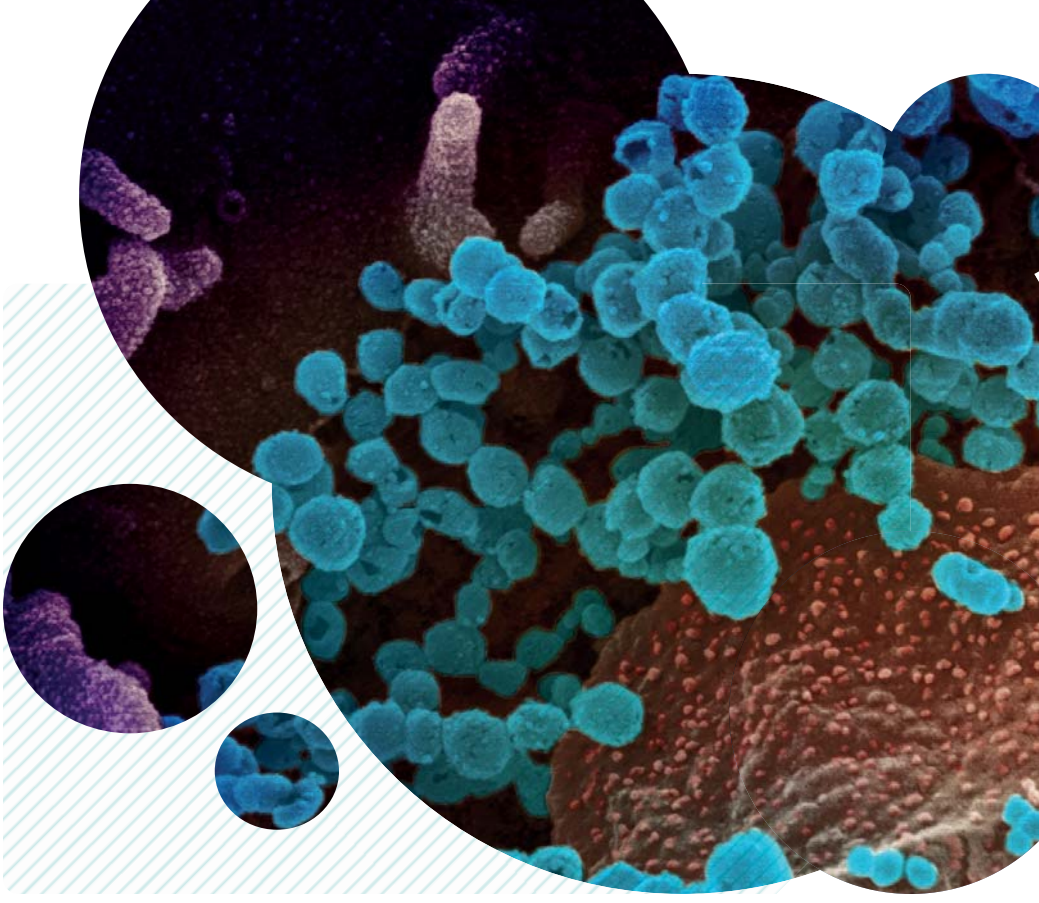
Researchers at MIT have identified a powerful antibiotic that can kill drug-resistant bacterial strains – using a machine-learning algorithm (1). The compound has been named halicin, after the fictional AI system, HAL, from "2001: A Space Odyssey." The computer model responsible for identifying the potential of halicin can screen over a hundred million compounds in a matter of days.

When tested in mice, halicin cleared Acinetobacter baumannii within 24 hours; prior to the team's experimentation, there was no known treatment for this bacteria, which causes serious infections of the lungs, blood, and brain. The compound was also shown to treat Clostridium difficile and Mycobacterium tuberculosis. Halicin disrupts the electrochemical gradient of bacterial cell membranes; if the gradient breaks down, the cell dies. According to the researchers, bacteria should find it very difficult to develop resistance to such a killing mechanism.

Reference

1. *JM Stokes et al., Cell, 180, 688-702 (2020).*





A Molecular Advantage

Using advanced diagnostics to develop and administer 2019 novel coronavirus treatment

As rapidly as the 2019 novel coronavirus (2019-nCoV) outbreak is growing, so too are the efforts to combat its spread using diagnostic technology. The newest player on the block? Molecular diagnostics, which aim to detect low levels of virus in the blood to yield faster, more effective infection detection. The creators of these new diagnostics hope that their tools will both assist with the development of new antiviral treatments and assess their effectiveness in individual patients, allowing earlier intervention and potentially slowing the global progress of the disease. We spoke to Irene Song, Global Product Manager at GenScript, to learn more about these diagnostics.

How does the 2019-nCoV outbreak compare to previous viral outbreaks?

The new virus has a longer incubation time than SARS and more closely resembles MERS – but it has less obvious symptoms than either previous virus, making diagnosis harder.

How can molecular assays help virus-affected countries?

To use 2019-nCoV qRT-PCR detection as an example, the assay provides a method to detect the virus even at a very low level, leading to the possibility of detection at a very early stage. A one-step multiplex qRT-PCR assay typically takes one hour after RNA extraction and can test hundreds of samples per run, potentially speeding up diagnosis and helping to reduce the spread of disease.

Because the virus is highly contagious and can cause a variety of symptoms, identifying infected individuals not only helps to provide appropriate medical treatment, but also significantly decreases the potential for transmission. Researchers can also use molecular diagnostics to evaluate the efficacy of a treatment by quantitatively measuring virus levels.

The FDA reviews and approves many molecular diagnostics every year. Many of these diagnostics test how different biomarker mutations relate to treatment outcomes during the clinical trial stage. Such experimental data will provide guidance for healthcare professionals to select suitable treatment plans for 2019-nCoV and beyond.

What do you see in the future for molecular diagnostics?

Molecular diagnostics is triggering a healthcare evolution toward personalized medicine. More and more healthcare professionals use molecular diagnostics to select appropriate treatments for patients. The application of nucleic acid sequencing technologies (such as whole-exome sequencing, targeted sequencing, or single-cell sequencing) plays an extremely important role in studying chronic, metabolic, and genetic diseases, as well as in recognizing the pathologies of infectious diseases.

In recent years, genomic panels have been used widely in cancer companion diagnostics to help healthcare professionals determine whether a treatment is suitable for a particular patient based on their disease-related mutations. They can also reveal the genomic information of a novel pathogen to help develop rapid diagnostics or even preventive vaccines. In the future, personal and clinical genomics will play a major role in assessing people's health risks, ancestry, and treatment plans based on both disease-related mutations and patients' genetic backgrounds.

The combination of vast genetic information and other healthcare data may help to predict the most suitable health plan for each patient – quite different from our current evidence-based practice. This shift could be the most strongly felt near-future benefit of molecular diagnostics.

Kuhner shaker

Reliable scale-up
from lab-scale
to production

SB10-X

ISF1-Z Peltier

Adolf Kühner AG
+41 61 319 93 93
www.kuhner.com

Scale-up
while maintaining the quality

The consistent hydrodynamics driven by Kuhner shaking machines allow for an efficient scale-up from microtiter plates to shake flasks and production scales. Our orbitally-shaken bioreactors (OSB) for single-use bags expand the range of shaken cultivations up to 2500 L.

You will find further information at:
www.kuhner.com/en/kuhner-technology/scale-up.php

achieve your goals with Kuhner shaker

In My View

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

Regulate with the Times

Ancillary material quality has become critical to the clinical advancement of cell and gene therapies. We need a regulatory framework that ensures safety, while also recognizing the growing cost burden on suppliers

By Claudia Zylberberg, Co-founder, Chief Executive Officer and President, Akron Biotechnology

How can we manufacture cell and gene therapies in a safe and cost-effective manner to treat as many patients as possible? It's the key question facing the cell and gene therapy industry right now. Ancillary materials are an increasingly important factor in the cost and safety of these new therapies. Unlike traditional small molecule medicines, cell and gene therapies cannot be sterilized before release. And that means companies must strictly qualify their ancillary materials as part of their effort to ensure patient safety, which comes with a substantial cost burden.

There is often variability among ancillary materials, which complicates efforts aimed at product characterization, specification, and quality management. The variability is largely due to the fact that, traditionally, ancillary materials were used primarily in a research environment, where requirements for material consistency, traceability and reliability are not particularly high. As therapeutic options have matured and moved to the clinic, these materials are now being placed under greater scrutiny by regulators.

Though there are several independent frameworks or guidelines that manage the quality of ancillary materials (examples include a Technical ISO Document led by the Standard Coordinating Body (SCB) with the participation of Japan, the UK, Germany and the US, among others, as well as the guidance set forth in USP Chapter <1043>), there is no official regulatory oversight. As a result, ancillary materials are produced according to different interpretations of "manufactured under GMP."

Regulators recognize the importance of ancillary materials to the safety of the final product, and so they are quite stringent in their recommendations for which raw materials ATMP

"As therapeutic options have matured and moved to the clinic, these materials are now being placed under greater scrutiny by regulators."

manufacturers should use. For example, the raw materials used in cell and gene therapies are complex in and of themselves – some are even pharmaceutical products, such as Interleukin 2 (aldesleukin). Regulators say that if you can use a pharmaceutical product instead of a reagent, then you should do so. But this means involving physicians and pharmacies, which creates a more complex supply chain, and further drives up costs. Another example is Human Serum Albumin (HSA). Regulators will often ask for injectable-grade HSA, even when it is only used in the manufacturing process (i.e. not as an excipient of the finished product) – again, increasing costs.

We need a way to balance quality with cost of goods. In some cases, it may be preferable or necessary to use ancillary materials produced in compliance with GMPs, including pharma-grade materials. However, developers may be able to control manufacturing costs without undermining safety or regulatory compliance in the case that a material presents a lower risk profile. Greater clarity and harmonization is needed to create a shared understanding of what constitutes a risk-based approach to ancillary material production and sourcing. The ISO technical document was a good start, but we need to go one step further.

My colleague, Oliver Ball, and I recently set out a framework for how we might go about regulating ATMP ancillary materials (1). In our article recently published in Cytotherapy, we propose a staged approach to ancillary material quality that progresses according to the user's quality requirements (for example, throughout clinical development phases), implementing additional aspects of GMP compliance and a greater degree of control at each stage.

"Our aim is to kickstart a discussion. Does our framework make sense to the rest of the industry? If so, great, but how can we make it a reality? If not, then what can we do to improve it?"

To briefly summarize, the framework is divided into three main stages: Development, Engineering, and Conformance. Ancillary materials produced under the first stage of development should be supplied for research use only – their manufacturing processes are in early stages of development, based on prior technical knowledge and pre-existing development work, and operate on a small scale. Moving into the second stage (engineering), manufacturing processes will be better optimized, with SOPs in place from previous experience in undertaking development runs, and a few changes will be made (although still acceptable in-process or between batches). Finally, the third stage of ancillary material quality represents close compliance to GMP principles and would usually operate on a larger scale. SOPs developed from the experience of performing engineering runs would be fully established and implemented.

Our belief is that suppliers will welcome this kind of approach because it relieves their pressure to invest in quality early – instead, they can invest progressively as the market expands. In other words, as manufacturers grow and move through the clinical stages, suppliers will invest in the quality of their ancillary materials in tandem. When a cell and gene therapy manufacturer begins discussions with regulators, the regulators will know that the supplier is working towards GMP and has documentation to support that.

We are currently in discussions with industry bodies to see if there's a way to create a webinar or white paper to further develop this staged approach to GMP ancillary materilas. Our aim is to kickstart a discussion. Does our framework make sense to the rest of the industry? If so, great, but how can we make it a reality? If not, then what can we do to improve it?

The existing guidelines developed by the ISO and others have worked well, but I believe the industry has matured, which means the regulation must also mature. Our hope is that our proposal will provide a starting point for the development of a regulatory framework that recognizes the important downstream effects ancillary materials have on therapies that cannot be sterilized, while remaining attentive to the commercial realities facing this emergent industry.

Reference

1. *O Ball and C Zylberberg, "Towards a common framework for defining ancillary material quality across the development spectrum", Cytotherapy, 21, 1234–1245 (2019).*

SPECIAL SERIES
Advanced Medicine

Manufacturing by Design

The gene therapy industry needs to reduce manufacturing costs by orders of magnitude. Let's start by optimizing cell lines, improving transfectants, and optimizing downstream purification.

By Frederic Revah, Chief Executive Officer, Genethon

Thinking back as recently as 2010 and 2011, there were only a handful of organizations with serious intentions of bringing gene therapy products to the market. I remember when pharma companies and venture capitalists used to dismiss gene therapies as too complicated, risky and inefficient.

Things have certainly changed. Close to $9 billion was invested globally in cell and gene therapies in 2018. Much of this has been driven by companies focusing on rare genetic diseases, which represent a relatively straightforward target if a single gene is responsible. These first "cures" have demonstrated that gene therapies can be effective and commercially viable.

Another factor in the (re)birth of the gene therapy field was the development of appropriate vectors (lentiviral and AAV, for example), which made commercial gene therapy possible. Despite the progress, however, manufacturing remains a key limiting step for widespread patient access. And so the next frontier for gene therapy is all about overcoming such manufacturing challenges.

In many cases, companies rush into manufacturing without realizing how important it is to the success of the product. Some question the validity of "the process is the product," but I believe it is. When you embark on a gene therapy program, of course, you have to consider the quality of the design and preclinical studies to demonstrate efficacy, but you also have to seriously consider how you will manufacture the product. And you must be aware that any change in the process may affect the structure of the product, necessitating preclinical and clinical bridging studies.

Most will be familiar with QbD, but what about MbD – manufacturing by design? If you switch from one manufacturing technology to another, the molecular nature of your vector may also change. So deciding which technology to use and how you will use it early in development is key in gene therapy.

I believe there's scope for improving gene therapy manufacturing across the whole value chain. Firstly, the viruses used in gene therapy are assembled in cell lines, and when you look at the productivity of the cell lines that are used today in terms of protein quantity, it's far lower than you might get for the production of an antibody. Creating stable systems has been the holy grail of expression technology for the past 30 years and we're still far away. If the industry as a whole can make greater strides towards stable systems, then the cost of manufacturing will fall.

Secondly, much of the transient transfection discussion focuses on the efficacy of transfection. Here, the role of the starting materials, the transfectants, is key and there is a need for the development of new and improved transfectants.

Finally, there is scope to increase yields through improvements in downstream purification steps, particularly capacity and separation so that viral species can be purified more precisely. Put simply, gene therapy preparations are mixtures of viruses, full and empty particles, together with contaminants from cell media. Analytical tools are the means by which manufacturers identify and quantify these different species at different steps – and, if these can be improved, efficiencies will increase and costs will go down.

These are some elements companies should be working on to improve productivity. Today, the cost of manufacturing for a single dose can be several hundreds of thousands of dollars. Our aim should be to reduce this by orders of magnitude in the coming years.

I am hopeful, especially when we look at the monoclonal antibody field, that it can be done. I can remember clearly how limiting the manufacturing technologies and processes were for antibodies 20 years ago. In contrast, just look at how seamless these processes are today. I have no doubt we'll make progress – we already have. Nobody knew how to manufacture treatments for neuromuscular indications a few years ago, taking into account the very important quantities necessary. Today, processes are available – at least for clinical trials. But to make these therapies commercial realities for the most common indications, we must continue to innovate in manufacturing.

MAXIMIZE EFFICIENCY
You'll find the solutions here.

NEW TECHNOLOGIES
You'll see innovation here.

LEARN FROM EXPERTS
You'll learn from subject matter experts here.

ACCELERATE TO MARKET
You'll find everything you need, from science through commercialization, to cost effectively develop and manufacture product here.

Experience science through commercialization

SAVE THE DATE
APRIL 28-30, 2020
JAVITS CENTER, NYC

NEED TO ATTEND? NEED TO EXHIBIT?
Register to attend OR submit to exhibit: INTERPHEX.COM

INTERPHEX

PDA Premier Association Sponsor


110
12ml
98
10ml
87
8ml

NEGLECTED TROPICAL DISEASES: *Your Attention, Please*

Patients. The pharmaceutical industry often talks about patients – and many company websites are full of great photos that emphasize patient centricity. But how do pharma companies measure up when it comes to patients who suffer from emerging pathogens and neglected tropical diseases? In some cases, treatments are available in wealthy markets (often marketed to travelers and holidaymakers) and yet, in poorer countries, people have to rely on altruistic research and donated drugs. Fortunately, select pharma companies are putting the needs of people ahead of profits.

By Stephanie Sutton

Samer Baher Mikhael takes Zithromax as part of a mass drug administration to combat trachoma near Matay, Minya Egypt. *Image credit: Sightsavers/Sima Diab*

Making Life

A LITTLE BIT SWEETER

Eliminating infectious diseases that lead to blindness in Africa – an eye-opening view from the frontlines

WITH SIMON BUSH, DIRECTOR OF NEGLECTED TROPICAL DISEASES, SIGHTSAVERS

The impact that neglected tropical diseases can have on communities really hit home for me in 1999. At the time, I was the Regional Director at Sightsavers for West Africa. I went on a field trip to Mali, where I traveled to a village a few hours outside of Bamako. Half of the village's population was blind due to onchocerciasis – otherwise known as river blindness.

River blindness is caused by a parasitic worm (Onchocerca volvulus), which is transmitted by bites from infected blackflies that live by rivers and streams. In the body, the worms produce embryonic larvae that migrate to the skin and eyes. Skin changes are a common symptom, but it's also possible for people to develop eye lesions that can lead to permanent blindness.

Sightsavers has been working with neglected tropical diseases for years, particularly those that cause blindness, like onchocerciasis and trachoma, but reading about these diseases and seeing the impact first-hand is very different. I was particularly shocked by the number of young people who were affected by the disease, including children. In this particular village, many able-bodied men and women were affected – and, as a result, the community was unable to farm.

There is no vaccine or preventative medicine for river blindness, but there is a treatment (ivermectin). At the time, treatment had been rolled out in numerous areas thanks to donations from Merck, but this particular village had missed out – despite the fact that nearby villages were being treated. It made me realize how important total elimination is. It's not enough to help some villages – patients everywhere need access to medicine.

KEY *milestones*

Fortunately, we have made progress. In fact, we've hit some incredible milestones since the London Declaration on Neglected Tropical Diseases in 2012, which aspired to control or eradicate certain diseases by 2020. Today, the blinding impact of onchocerciasis has been reduced thanks to mass drug administration programs – and we're even talking about the elimination of disease transmission in a few years' time. According to WHO, around 217.5 million people are at risk of contracting river blindness. Around 20.9 million people are actively infected; 14.6 million people are affected by the skin disease; and around 1.1 million people are living with blindness or visual loss. Ninety nine percent of those people live in rural Africa. Thanks to the donation program by Merck, nearly 152 million people were treated globally in 2018. Sightsavers helped support the treatment of around one in four of all the individuals treated that year.

But the program could not have happened without the donated drug. Incidentally, ivermectin was one of the first drugs to be donated by a pharma company – and Merck has committed to the donation program for as long as required. In Nigeria last year, transmission of the disease in two large states was interrupted. And that represents a huge success, because Merck and Sightsavers have been treating people in Nigeria since the 1980s. We still need surveillance systems to ensure the disease does not return, but it's an incredible achievement. It also shows how long it takes to make progress and achieve elimination or interruption of transmission.

There have also been major milestones in trachoma – another infectious disease that can cause blindness. It causes roughening of the inner surface of the eyelids, and can lead to enormous pain and blindness. I've visited communities affected by the disease and patients have told me that it is like having sand in your eye; every time you blink, your eye is scratched. A key milestone for this disease was the Global Trachoma mapping project, which was launched in December 2012 and completed in January 2016. It sounds basic, but to achieve elimination, you first have to map out where you need to apply donated drugs and other programs. It was the largest infectious disease mapping program ever undertaken and has really pushed the trachoma elimination program forward.

Pfizer has been donating the antibiotic Zithromax to treat trachoma for around 20 years now through the International Trachoma Initiative (Sightsavers is one of the many partners in this initiative). It's a great example of a public-private partnership. It was first established in 1998 – with Pfizer initially committing to 10 million doses. Today, they've delivered over 897 million doses. And here's another fantastic achievement: in 2018, Ghana became the first sub-Saharan African country to eliminate trachoma.

Donating drugs is a proven approach and is part of the WHO's SAFE strategy for tackling trachoma – surgery, antibiotics, facial cleanliness, and environmental improvement. Trachoma is still prevalent in 40 countries – and to achieve elimination, these countries are reliant on Pfizer's free antibiotics. Pfizer has extended the donation until 2025. Another amazing statistic: because of the donations and all of the fabulous partners working in trachoma, the WHO announced in 2019 that the people at risk from trachoma had fallen from 1.5 billion people living in trachoma endemic areas to just over 142 million in 2019 – a reduction of 91 percent! And though it may not be the elimination that we had hoped to achieve by 2020, a 91 percent reduction is still an incredible achievement.

IT *matters*

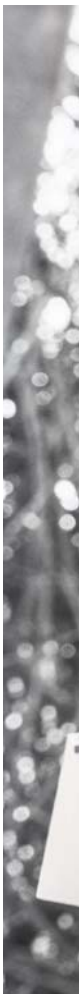
There is no doubt that the field of neglected tropical diseases is challenging. It's one thing to aim to reduce the incidence of disease, but elimination is incredibly difficult, especially once you've reached over 90 percent of your target population and need to find those last few patients – who may be located in remote areas, or areas of conflict with security risks for aid and healthcare workers. For pharma companies, donating important drugs for years also comes with financial implications. But now, more than ever, it is important that all stakeholders – governments, pharmaceutical companies, charities and community groups – work together to ensure donations are sustainable and delivered safely. We don't just want to control diseases like trachoma and river blindness – we want to eliminate them. When you are aiming for control it doesn't matter if you don't hit your target one year because you can probably catch up the next year, but when you are striving for elimination, you need to consistently hit and exceed your target every year.

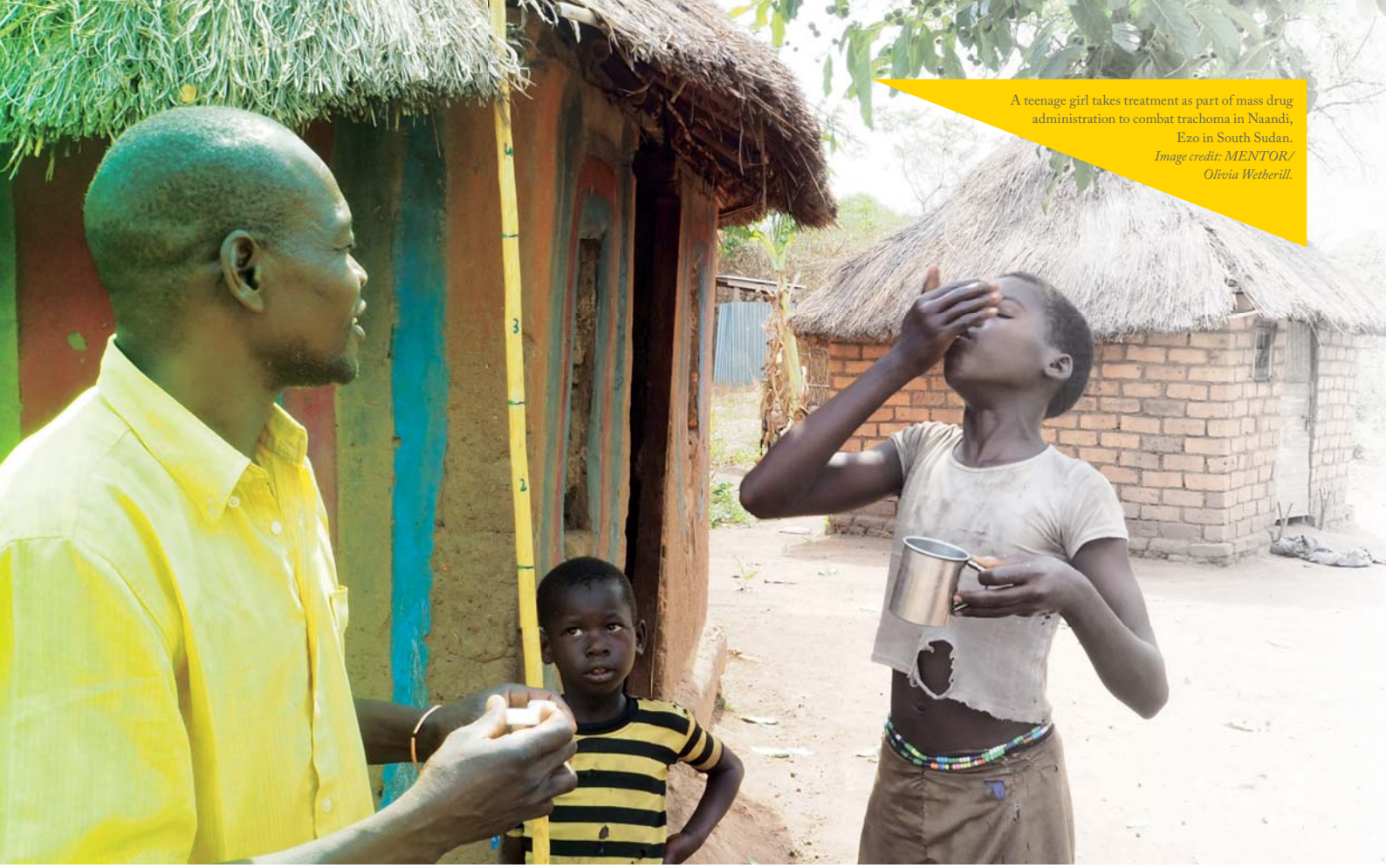
Recently in Ghana, where I live, I traveled to some communities where Sightsavers has been distributing drugs for river blindness and lymphatic filariasis. One lady told me that our work makes life sweeter. I've read a lot of case studies about our work and how it empowers workers and communities to increase agricultural production, but when somebody simply tells you that your work makes their life sweeter, it really means something.

In another village, I spoke with the community leaders about blinding trachoma and they simply said, "We don't have that disease anymore."

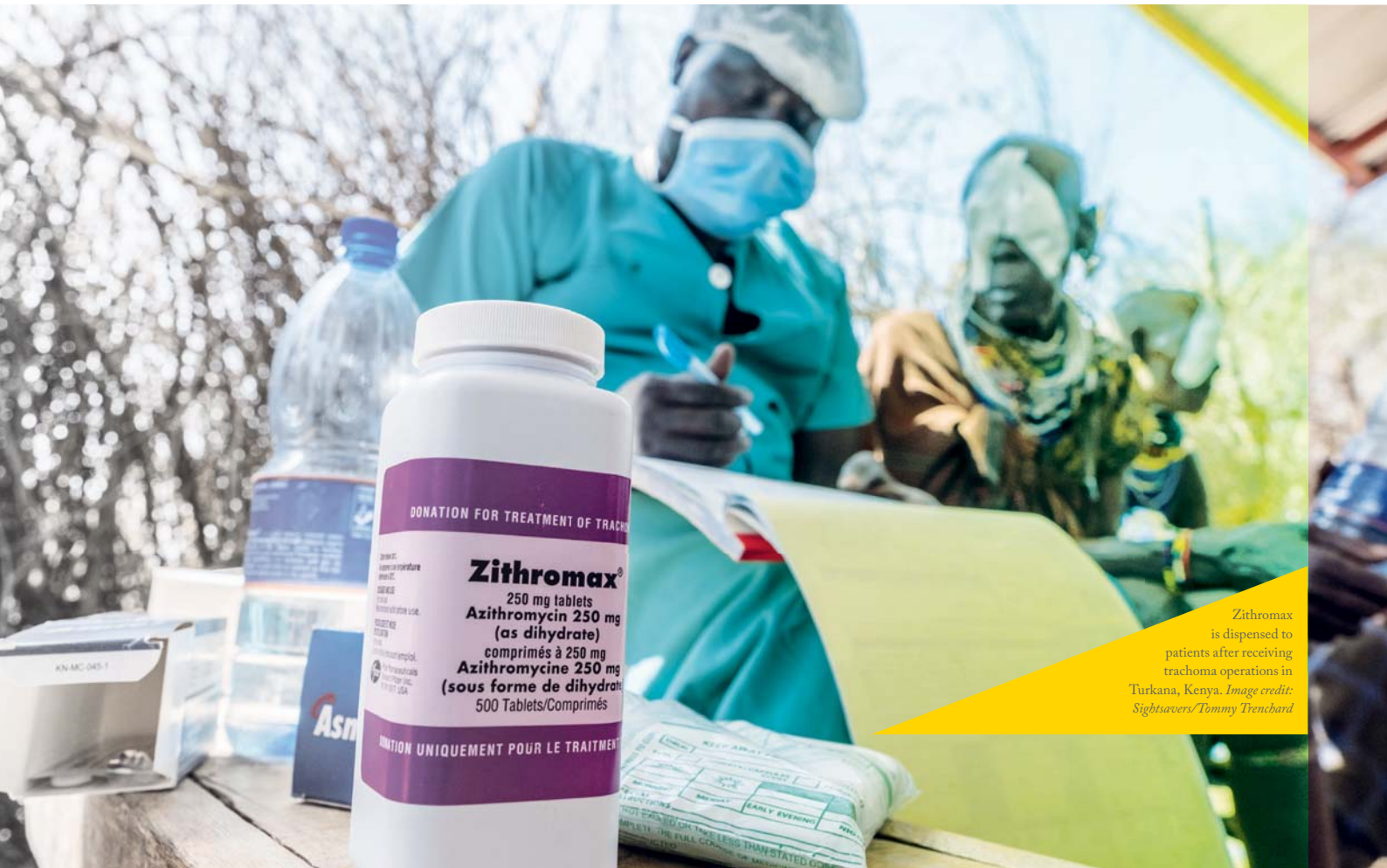
Without drug donations, we could never have come this far.

For those of you who are removed from direct interaction with the patients afflicted by tropical diseases – for example, policymakers or professionals in pharmaceutical companies or research organizations that develop or donate drugs for neglected tropical diseases – please remember that your work really matters. It is making a huge difference to human lives.





A teenage girl takes treatment as part of mass drug administration to combat trachoma in Naandi, Ezo in South Sudan. *Image credit: MENTOR/ Olivia Wetherill.*



Zithromax is dispensed to patients after receiving trachoma operations in Turkana, Kenya. *Image credit: Sightsavers/Tommy Trenchard*

Community drug distributor Hajiya Luba Garba from Sokoto in Nigeria with her 'dose pole', a measuring stick that determines how much medicine to give someone based on their height. *Image credit: Sightsavers*

CRUCIAL *Cartography*

Julie Jenson, Director of International Product Access at Pfizer, expands on the company's work with Sightsavers – and how mapping disease prevalence ensures that resources reach the right areas

Tell me how Pfizer first started to work with trachoma and Sightsavers…

The company has a long-standing commitment to make the best use of our resources – including our people, products, and funding – to help build healthcare capacity, expand access to medicines, and offer community support through corporate citizenship initiatives.

The International Trachoma Initiative (ITI) was established in 1998 by Pfizer and the Edna McConnell Clark Foundation, with the intent of eliminating trachoma by 2020. Today, approximately 163 million individuals are at risk for trachoma, and the disease accounts for an estimated $3-6 billion in lost productivity per year.

As well as managing Pfizer's donation of antibiotics to the program, ITI collaborates with stakeholders to implement the WHO's recommended "SAFE" strategy for trachoma control.

Throughout the lifespan of ITI, it's been challenging to predict the prevalence of disease, with limited data available on disease prevalence in many rural areas. It turn, this has made it difficult to quantify the need for antibiotics at any given time. Sightsavers has been instrumental in helping us solve this, leading the Global Trachoma Mapping Project.

Using smartphone technology, the Mapping Project allowed fieldworkers to identify communities in need and send the data back for analysis faster than ever before.

Over the course of the Mapping Project (2012 to 2016), 2.6 million people were examined across 29 countries. For the first time, this initiative provided us with real time data on where antibiotics were needed, and a clearer picture of the volumes required.

With this evidence in hand, Pfizer was able to develop a strategy that saw an expansion in production, and an increase in medicine output – from 50 million to 120 million doses between 2014 and 2018.

The ITI was also able to use this data to make earlier interventions. Data transferred from the field in real time allowed the ITI's expert committee to approve and dispatch donated antibiotics more quickly, which had a rapid impact on communities affected by trachoma.

What achievements in this area are you most proud of?

We're proud of the program itself – for the many partnerships it has fostered with over 100 government and non-government organizations around the world, including Sightsavers.

Most importantly, we're proud of the progress we have made collectively – treating in excess of 100 million people across 33 countries, and seeing Oman become the first country to achieve validation of elimination by the WHO in 2012. Nepal became the sixth country to be validated by the WHO in 2018, joining Oman, Morocco, Mexico, Cambodia and the Lao People's Democratic Republic.

For donated drugs, how do you ensure programs are sustainable?

Sustainability is important to build into any program. In this case, the project has a clear timeframe, beyond which all the partners hope there will be no need for further medicine.

In addition, the ability to plan is important – to be able to understand the quantity of donation required, at what time, and where in the world. This is why the mapping project was so instrumental in our ability to deliver.

Finally, the role of partnership should not be underestimated. Strong government and NGO partners can ensure that any donations are used effectively in the populations that most need them. And this in turn gives us the confidence that our efforts are having an impact.

It's been 8 years since the London Declaration; what have been the key milestones?

The London Declaration brought together all stakeholders (governments, NGOs, donors, pharmaceutical companies, academic institutions, and so on) to support the control, elimination, and eradication of at least two NTDs by 2020. There are 18 NTDs under the WHO definition in total – ten of which are benefitting from medicine donations from across the industry, including Pfizer's efforts to eliminate trachoma.

For us, it's good to see the progress made on the fight against trachoma, with countries achieving elimination and a notable slowing in the demand for antibiotics in the program. However, our goal was worldwide elimination of trachoma by 2020 – and while we expect to come close, its expected there will be pockets of disease that remain beyond 2020.

Pfizer has extended its donation through 2025, should it be needed, to ensure antibiotics will be available to help all endemic countries reach their targets to achieve the worldwide elimination of trachoma.

Lending
A HELPING HAND

Maria Elena Bottazzi (Co-Director at Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine) and Bart Fryszczyn (a process development scientist at Merck) tell a tale of a successful partnership between academia and industry – and how collaboration is essential when it comes to helping the world's poorest and tackling some of the most debilitating infectious diseases

Schistosomiasis is a tropical infection primarily caused by parasitic worms. The mortality rate is low, but it affects millions of people in the poorest populations in the world and causes huge burdens of morbidity. It is difficult to diagnose because there are often few symptoms early on but, over time, the worm causes damage to the bladder, kidneys and liver, causing malnutrition, inflammation and pain. It affects people of all ages, including children, and for women, it can cause complications with pregnancy. The estimated number of people infected is around 250 million, but some studies have estimated that half of the population in Africa could be infected.

Maria Elena Bottazzi has been working on the development of a vaccine for this disease. "I grew up in Honduras, which has a high burden of neglected tropical diseases. I obtained a degree in microbiology and clinical chemistry, but it was parasitology that interested me the most. When I did my PhD in the US, I focused on molecular biology, immunology, translational medicine and vaccines to tackle parasitic diseases. For the last two decades, I've been working to develop appropriate and affordable global health technologies, with a strong focus on vaccines for various neglected and emerging diseases, including schistosomiasis."

Very few for-profit entities have any focus on developing interventions for neglected tropical diseases. The Center for Vaccine Development in Houston aims to develop important interventions that no one else is focusing on, including vaccines for human hookworm disease, schistosomiasis, Chagas disease, leishmaniasis, onchocerciasis, and coronaviruses – to name just a few.

"When we started our vaccine programs almost two decades ago, we evaluated the diseases we should be working on and schistosomiasis came out as one of our top priorities," says Bottazzi. "There is a drug that can treat schistosomiasis (praziquantel), but it does not prevent a person from becoming reinfected. We need an integrated and complimentary approach because drug treatment alone is not enough. We need a vaccine."

MUSING ON *Academia's Changing Times*

By Maria Elena Bottazzi

There is a view that academics don't have a lot of interaction with biotechnology or pharma entities, but academia is beginning to play a much more important role in the drug development ecosystem by helping to translate basic research into real products. And that's because the nature of how the industry develops treatments is changing – with many pharmaceutical entities wanting to de-risk their investments and collaborate earlier with more academic institutes to not only jointly develop global health technology but pick up the development once the technology has already shown proof of safety and, in most cases, even efficacy.

This shift also brings challenges. Our Texas Children's Hospital Center for Vaccine Development in Houston has more than two decades in operation, but how do we shift from an academic mentality to becoming an almost pseudo-biotech company when we are a non-profit developing products that will never make money? We've had to develop not only new infrastructure, including setting a robust and strict quality system with quality assurance and regulatory support, but also evolve our scientific mindset to think about the critical path with the goal of advancing serious products that can one day be licensed. Therefore, our students, scientific staff, and lead investigators, who can certainly drive hypotheses and conduct academic work (which includes lecturing and teaching), also had to learn a new way of thinking.

But it can be a wonderful world to work in. One of the things I love about my job is that it spans both worlds. I am a professor, but I also have the opportunity to navigate the biotechnology sphere and forge unique collaborations with industry; for example to really move our products forward. At times, it's as if I was embedded in a big pharmaceutical company.

At our Center for Vaccine Development, we do basic science, but we have created a niche to efficiently transform that basic knowledge into translational research, develop products, and even perform sophisticated manufacturing and technology transfer processes. We collaborate with more than 40 global partners on regulated clinical studies and even submit our own regulatory applications. It's only through transformational change and collaboration that we can really deliver these much-needed interventions for neglected tropical diseases.

THE *manufacturing conundrum*

Progress on the development of a vaccine has been going well. Bottazzi and colleagues developed a bench-scale process suitable for technology transfer and GMP pilot scale to rapidly transition the vaccine into early clinical trials. But when it comes to planning for scale-up of GMP manufacturing, there were clear challenges. In particular, the pilot process they had developed had low recovery rates, long processing times, and involved multiple unit operations. A large membrane area was also needed to ensure sufficient clarification of the fermentation broth with its relatively high viscosity and suspended solids content. To improve the process, the vaccine center scientists in Houston have been working with Merck, a Darmstadt/Germany-based science and technology company, to assess, re-evaluate, streamline and design an improved large scale manufacturing process for their vaccine candidate.

"The story behind my involvement in this project really complements Maria's experience," says Bart Fryszczyn, a process development scientist at Merck. "My education background lies in protein science (incidentally, I did my graduate work at Baylor College of Medicine), and when I finished my PhD studies, I was really excited by the idea of going into industry and helping scientists design manufacturing processes for biologics, such as vaccines and other molecules. Today, I work with Merck in their technology management division. The purpose of this division is to share our knowledge such that it can drive adoption of our company's products. Put this way, it sounds a little selfish, but we recognize that our organization is made up of hundreds of engineers and scientists globally, so collectively we have a lot expertise in manufacturing outside of our portfolio of products to give. We've worked with vaccine processes for decades."

As well as working with many for-profit companies, Merck also gets involved with smaller projects targeting huge needs, such as treatments and vaccines for neglected diseases, which are supported by Merck's M Lab Collaboration Centers. The Center for Vaccine Development in Houston has been collaborating with Merck since 2017 – and Merck itself has a keen interest in schistosomiasis. Merck has donated over 1 billion tablets of praziquantel to the WHO since 2007 for the treatment of school aged children. In 2019, as part of its Pediatric Praziquantel Consortium project, Merck Healthcare initiated a Phase III clinical trial in Kenya to evaluate a new pediatric formulation of praziquantel to treat schistosomiasis in pre-school age children under the age of six. The trial will also be conducted in the Ivory Coast.

"Praziquantel has been donated by Merck for years," says Bottazzi. "After meeting Udit Batra, the CEO of the life science business of Merck, we were put in touch with the wider Merck network to assist with our vaccine process development work."

Bottazzi's group had three aims in mind for the collaboration: i) shape the collaboration in a way that raises awareness of the importance of new interventions for the disease and demonstrates the benefits of collaborations between a for-profit and a non-profit, ii) develop a global technology with a process that is affordable and accessible to manufacturers, especially those in the different countries that would urgently need this vaccine, and iii) take advantage of new innovations, such as new purification platforms, resins and filters, and apply them to new manufacturing processes.

For any vaccine or new treatment to be successful, the manufacturing process must be scalable, transferable and economically feasible. "At the onset of the collaboration, we reviewed the purification process for the molecule," says Fryszczyn. "This is the most important aspect of manufacturing because it is imperative that a continuous evaluation of impurities is documented during the development of biologics. This particular vaccine was being made using a yeast expression system. Although the group had a process that worked at the bench- and pilot-scale, a lot of aspects could not be implemented at a full-scale industrial manufacturing level effectively. We identified the 'low-hanging fruit' – the weakest parts of the process where we could have a high impact. One of the main areas was clarification and concentration of the molecule. The process was barely efficient and time consuming, but we redesigned it using a continuous process to make it faster with less expenditures."

"As well as doing an intellectual evaluation and redesign of the process on paper, we tested some new technologies for clarification," adds Bottazzi. "We were able to increase the recovery rate from 31 to 42 percent. We were also able to reduce the timings and reduce process costs by 36 percent – and the process is more reliable too."

The vaccine has gone through a first-in-human study in a non-endemic area (USA) and in Brazil (an endemic area), which was supported by the US National Institutes of Health (NIH). "We have a very robust safety profile for this vaccine candidate," says Bottazzi. "Currently, with funding from the Department of Defense of the US – because schistosomiasis not only affects populations living in endemic areas, but also areas where the US army is deployed. We are collaborating with the Vaccine Research Center at George Washington University and Makerere University in Uganda, to evaluate this vaccine in populations in Africa".

THE BUSINESS *of compassion*

With the improved manufacturing process, Bottazzi is hopeful the vaccine center can receive funding to re-engage manufacturing companies to scale up and perform a new GMP campaign using the revised and improved process. This would include engagement with the regulators providing evidence that the new process generates a vaccine candidate that maintains the same attributes and characteristics and bridge this material into the ongoing clinical development plan. From there, they can progress into more advanced clinical and manufacturing development stages.

But a non-profit institute cannot bring a vaccine all the way through advanced manufacturing and clinical development alone. The Vaccine Center in Houston will need help from manufacturers in the areas where this disease is endemic, such as Brazil, China, India and Africa. "It is sometimes difficult to find the right partners who are also passionate about the cause," says Bottazzi. "With neglected tropical diseases, you don't just need high scientific input; you also will require a high financial input. And this is where the industry still hasn't deciphered. What is the right business model for vaccines for neglected diseases? It is unlikely that a single institution would contribute and I think it has to be a combination of institutions, government, for-profit entities, and non-profit entities. We are working hard on this vaccine and eventually someone, somewhere is going to have to help advance it to the end."

Fryszczyn adds that the cost of altruistic work is one of the hardest things to reconcile in the industry. All traditional pharma companies perform work that can be described as for the greater good since it relates to health and wellbeing, but profits must also be considered. "I believe there should be more of a push for projects where profit is not a motivation," he says. "There should be more programs between governments and for-profit entities that allow commercial companies to help academia or small institutes to develop much-needed drugs for neglected areas. The burden of developing treatments for the world's poorest can't be on the back of a single organization. There needs to be more incentives that help more for-profit companies to get involved."

In a traditional business model, a vaccine is made and a company will evaluate how much it costs, how much it can be sold for, and what the revenues will be – and this revenue is easily quantified. However, it can be more complicated when you look at the value of an intervention that leads to improved human health without direct profits. "If you can prevent a number of people from becoming sick, they will have better health, healthcare costs would decline and the people can ultimately become more economically productive within their communities," says Bottazzi. "We are very interested in metrics around public health. In collaboration with Merck, we've built a business case and a value proposition for our schistosomiasis vaccine, but we also need to work with policy makers in terms of how this type of vaccine will be used in a vaccine delivery strategy. There is a huge problem with vaccine hesitancy right now and nobody wants to develop a vaccine that people will not accept and use. This is an issue that all of us connected with pharmaceutical development or global health have a duty to contribute to."

WHAT LESSONS
Have We Learned From Ebola?

And how can we ensure we are better prepared to develop new vaccines and treatments for future infectious disease outbreaks?

WITH JOHAN VAN HOOF, GLOBAL HEAD, INFECTIOUS DISEASES AND VACCINES AT JANSSEN

You visited Sierra Leone during the Ebola outbreak. What was the experience like?

Even if you are very passionate about a subject and eager to help by developing a vaccine, being in the affected area really adds a new dimension. It made me realize that this is about more than vials and vaccines – it's about people. It was very emotional to see the Ebola outbreak, how it paralyzed a country's economy and the social lives of its population. People could not shake hands. They had to take their temperature when they went in or out of a public place. There were washing and sanitizing systems everywhere. It was very disruptive, especially for a poorly resourced country.

What is the story behind Janssen's Ebola vaccine?

Between 2002 and 2014, a lot of the work was done by Crucell, which was acquired by Janssen in 2011. Our work began within the potential context of Ebola being used for bioterrorism. We wanted to provide protection against different filovirus species, including the Ebola and Marburg viruses. Crucell explored several vaccine candidates as they looked for better and better immunogenicity.

Much of the work was done collaboratively with different partners, including academia and the US Army. One of the many challenges was developing a standardized animal model because, in the absence of being able to conduct an efficacy study, you need to know if the vaccine has a reasonable chance of being protective in humans.

By 2014, we had a vaccine that was able to protect against lethal doses of filoviruses in animal models. The Ebola outbreak came around this time, and based on the sequence of the strain behind the outbreak, we knew that our vaccine should, in theory, provide protection. We decided to accelerate the development and made the decision in August 2014 to switch from developing a multivariant vaccine to a monovariant vaccine focused on the Zaire Ebola strain responsible for the outbreak. We also took the decision to partner with Bavarian Nordic on a booster dose for our vaccine – and by December 2014 we were in the clinic.

Thanks to various partnerships established in Europe, the US and elsewhere, we launched more than 10 clinical trials – Phase I, II and III – almost in parallel.

How does the vaccine work?

The vaccine uses a two-dose prime and boost regimen: Ad26.ZEBOV and MVA-BN-Filo to deliver Ebola GP transgenes to trigger an immune response. The first leverages our AdVac technology and the second uses Bavarian Nordic's MVA-BN technology. The doses are administered about eight weeks apart. Both vaccine platforms are based on a viral vector strategy, with AdVac using adenovirus serotype 26 and MVA-BN using Modified Vaccinia Virus Ankara; both of which are engineered to be non-replicative.

The nice thing about non replicating vectors is that side effects are less likely – we've seen this clearly in our clinical trials. More than 30,000 people have been included in trials so far and there has been no safety signal at all, which is very reassuring!

What was the biggest challenge during development?

By the time we were ready to go into large-scale efficacy studies in 2016, the Ebola virus had nearly disappeared. This was great news for the world but you can't demonstrate the effectiveness of a vaccine without exposure to Ebola, so there was a lot of discussion with regulatory agencies about how to advance this vaccine. They agreed that registration could be based on the immunological data that we observed in humans, as well as bridging data on the protective immune responses from animal models (non-human primates). Based on that, we agreed on pre-established success criteria.

What is the situation with Ebola and vaccines today?

The more recent outbreak has brought Ebola into the spotlight. Merck's vaccine (rVSV-ZEBOV-GP) has recently been approved and is being used in a ring vaccination campaign geared toward frontline health workers and close case contacts. We submitted registration for our vaccine in Europe in November last year, and I hope that a decision will be reached before the end of 2020. In the US, discussions with the FDA are still ongoing.

In parallel to this activity, with the support of health authorities in the Democratic Republic of Congo (DRC) a large scale vaccination study has started in Goma. The aim is to vaccinate up to 500,000 people in the region who could be seen to be at risk of exposure to Ebola in the future. We have donated up to 500,000 regimens of our vaccine to be used for this large-scale trial.

In July 2019, there was a fear of Ebola spreading into

Rwanda when two cases of the disease were reported in the DRC city of Goma, which is a major trading hub located near the border of the two countries.

Toward the end of last year, we received conditional approval for a vaccination regime in the Republic of Rwanda. Up to 200,000 people will be vaccinated in a government-led program – with a focus on those living at the border with DRC, and especially those who cross the border on a daily basis to work.

What were the biggest lessons learned during the Ebola epidemic?

The Ebola crisis triggered discussions around how we can be better prepared for these situations. The WHO has launched its R&D blueprint – a global strategy and preparedness plan that facilitates rapid R&D activity during an epidemic. Further, CEPi (Coalition for Epidemic Preparedness) has also been created to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks. CEPi has identified some pathogens and viruses that could potentially become threats, and there has also been a project on how we prepare for a situation where an unknown virus triggers a pandemic.

Overall, I think there is much greater vigilance about situations that could become a pandemic. With the coronavirus, for example, the initial scientific response has been rapid, with a focus on transparent data exchange. The first observations were made in hospitals in China in December and the full sequence of the virus has already been published, giving people the opportunity to start working on countermeasures. Meetings have already happened in Geneva too this year about how to drive standardization of the tools that will be used to help assess coronavirus vaccine candidates.

What other infectious disease areas is Janssen working in?

We're working in numerous areas, including TB (which although curable is still the world's deadliest disease), HIV and, more recently of course, the coronavirus. With the latter, we've started to construct vectors that could be candidate vaccines to evaluate in preclinical models in the coming weeks. We hope to be in the clinic with a coronavirus vaccine by the end of the year. We're also collaborating with academic partners at the Jenner Institute to screen small molecules for potential antiviral effect. We'll be focusing on molecules that have already been proven safe for humans, which should speed up development, if we get a hit.

ACCEPTING RESPONSIBILITY
For Global Health

Morningside Pharmaceuticals, a UK company based in Leicestershire, develops generic medicines, but has also been supplying global aid for almost 30 years. The company works through the private sector, ministries of health, and with large aid agencies, such as UNICEF, WHO, MSF and the Red Cross. We speak with Nik Kotecha, CEO of Morningside, to discuss why pharma companies have a responsibility to take the lead.

Why must pharma businesses do more to help developing countries?

Put simply: there is a real need, and it is the right thing to do. Access to safe medicines can be a big problem in some developing countries; pharma companies are responsible businesses and, therefore, should play a vital role by ensuring the supply of cost-effective quality medicines in all regions where there is need.

Beyond donating medicines or supplies, the pharma industry, working closely with local regulatory bodies, also needs to do more to regulate and remove counterfeit medicines from healthcare systems – especially in developing countries where the problem is highly prevalent. It is also important that medicines imported into developing countries are transported in a safe, secure, temperature-controlled way.

There is research to consider, too. Many communities in the developing world are still using older antibiotics, making resistance a big problem, especially in regions with a history of over prescribing. The pharma industry can invest in R&D to develop new molecules – and wouldn't it be great if this R&D could also take place in the developing world? Developing countries also need support in other aspects, such as technology transfer and knowledge and education concerning the use of newer drugs.

How can we make sure aid efforts are sustainable and controlled?

For all pharmaceutical manufacturers, there are times when stock comes close to its expiry date. If we donate products, we actually guarantee they will have a shelf life of at least a year to ensure maximum benefit to end users. We have set up systems internally where supply chain managers meet regularly to assess which products are nearing their expiry date. We also have registered aid organizations, which are approved as part of our quality management system. And that's important, because pharmaceutical providers need to ensure that aid organizations have the right licenses to handle medicines.

Even if your business is not able to make an overall obligation to supplying aid, please consider setting up systems and processes to make donations to licensed aid organizations.

Donations don't have to break the bank or involve millions of doses; can you provide examples of smaller but impactful efforts?

We have been working in partnership with aid organizations for a number of years and have made numerous donations of medical supplies. We recently donated antibiotics to treat 600 patients who were suffering from respiratory illnesses, such as pneumonia, at a health center in Malawi. We also donated 3000 packs of an oncology drug through International Health partners to treat cancer patients in a Palestinian Hospital – and that's our largest, by value, donation. The medicine, which can

be prescribed as part of a patient's chemotherapy treatment, was provided to the Shifa Hospital in Gaza, which is the only hospital in the territory able to receive cancer medicine.

We have also made a financial commitment to support the work of charities and NGOs. For example, we get involved with InterCare, a local charity in Leicester, UK. We funded InterCare's WDA (wholesale distribution authorization) online approved stock control system, which is approved by the MHRA, and helps the charity to track the recycled surplus UK medicines and healthcare goods it sends to rural health units in some of the poorest parts of sub-Saharan Africa. The digital system was the first of its kind since the organization was set up in 1974, and enables the charity to meet EU GDP standards in terms of tracking the aid right from the warehouse to the delivery of each health unit in Africa.

How can companies step up even more during an epidemic?

During an epidemic – with COVID-19 being a current example – hospitals and health centers in developing countries become overwhelmed very quickly. The supply of quality medicines can also be inconsistent, resulting in a huge urgency for more drugs to treat a sharp increase in patient numbers. We are a generic drug manufacturer – and generic drugs are in high demand with aid organizations. Generic medicines from the UK are some of the most competitively priced in the western world because of the NHS and the buying power that it has, which increases price competition. Products licensed by the MHRA are also deemed to be of very high quality – and patients in developing countries deserve high-quality medicines too.

During a crisis situation like this, companies have a role to play in providing larger quantities of medical aid, if they are able to. To support this, they should work in partnership with aid organizations (for example, charities, NGOs), which guarantee the products will be transported in the right way, so they have maximum impact when they reach the affected communities. If a manufacturing business has set up processes for providing aid, perhaps they can be adjusted to add more assistance when epidemics occur.

Providers also need to do more to react. I think this is something Morningside is very good at. For example, during the Ebola crisis, which developed very rapidly, we responded quickly and supplied a significant amount of healthcare products. This is the same if there is a natural disaster, where we work to source a wide range of quality medicines for supply within a short period of time. The more involved you are with aid, the better you become at responding because you have the right systems and processes in place.

Business

Economic drivers
Emerging trends
Business strategies

Digitalization Now

Digital technologies are here – but are they being used adequately?

The pharma industry could not operate without regulations – drug development is complex and regulations ensure companies pay adequate attention to all essential aspects, ultimately ensuring patient safety. But many also perceive regulations as stifling innovation. In its study, "Pharma Insights 2019", consulting firm MAIN5 found that 65 percent of processes in a pharma company are audit-focused; only 8 percent of processes are future oriented. Digitalization could have a huge impact on processes – if companies can overcome the challenges of implementation. We spoke with Tore Bergsteiner, Managing Director at MAIN5, to learn more about the survey respondents' attitudes to new technologies.

What were the most surprising findings of the study?

We were astonished by how massive the impact of digitalization could be in life sciences (90 percent of respondents said the impact of digitalization on the pharma and life science sectors is high or very high). However, processes in pharma are still perceived as being primarily audit-focused, or even just historically evolved. Even though the digital transformation is present, it is currently not matched with a substantial change in the processes and cultures within pharmaceutical organizations. In particular, pharma is a rather data driven business and we can see high potential in the value that could come from computational mass analysis of the large data repositories.

We assume that the situation will change in the next 2-4 years.

Given the highly regulated nature of the pharma industry, it is perhaps unsurprising that most companies operate from audit to audit. How do you think pharma companies can shift away from this mindset while still adhering to regulations?

Some organizations have already started changing. Rather than a culture of internal, written down over-regulation, some are moving towards the concept of establishing a quality culture by giving more responsibility to each individual employee. This movement is accompanied by establishing a guiding principle called lifelong learning. In pharma, we see that QA and HR are collaborating to establish global learning management systems.

Pharma has so much data at its disposal – why is it so challenging for companies to use their data?

There are probably three main reasons why it is so challenging to utilize data to achieve a real business advantage:

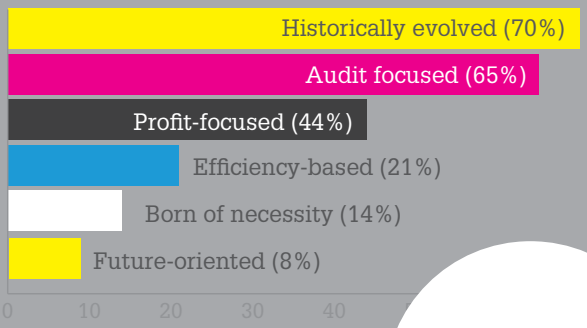
1. The data formats are not consistent across the repositories and can hardly be matched to automatically generate meaningful statistics or fully automated results.
2. The quality of the data has not yet been checked against the best way of using them. The data cannot be used for the intended goals, if the data accuracy is not assured.
3. Due to the complexity of the industry, we don't yet have the knowledge of how best to use data material. Companies realize that it might be a treasure – and it surely is – but most need a manual to really see the possibilities.

Other industries have been talking about the value of data and digital technologies for many years. How far does pharma lag behind?

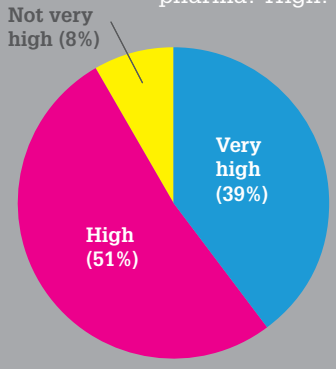
To be honest, I believe that most industries are struggling with the challenge that digital transformation brings. Some industries, such as insurance, energy, automotive, defense and retail, are discreet regarding the range of problems in their

DIGITALIZATION IN NUMBERS

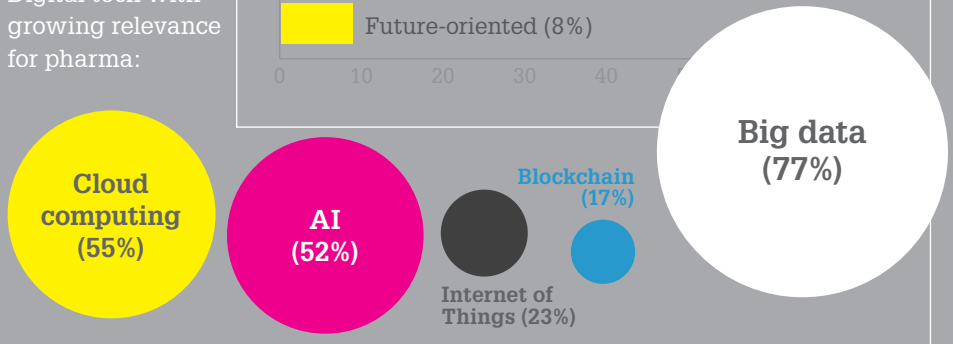
Processes in the pharma industry tend to be…



How high is the impact of digitalization on pharma? High!



Digital tech with growing relevance for pharma:



Main challenges faced by pharma as a whole

- *Product diversification and opening up of new growth markets*
- *Data protecion/ compliance with GDPR*
- *Expiring patent protection with the increase of generics*
- *Falling blockbuster profits*
- *Growing risk of counterfeit drugs*
- *Standardization of country-specific regulatory requirements*
- *Internet trade in drugs*
- *Grey and re-imports*

Top challenges that could hinder digital transformation:

- *Lack of digital knowledge among employees*
- *Legal regulations*
- *Compliance requirements*
- *Lack of compatibility between existing and digital processes*
- *Lack of involvement of employees in the process*

businesses. In general, however, industries such as banking and pharma have to cope with an enormous amount of regulation all over the world, while others are free to "just do it." It is hard to tell in terms of years how far the pharma industry may be behind, or how quick it may catch up. Certainly, the investments put into digitalization today will decide the market presence of organizations tomorrow.

For a company that is quite far behind – and operating from audit to audit – what are your top tips on how they can start to break the cycle?

The goal should be to create efficient and easy to understand processes without harming compliance. Sometimes it takes an outside eye to observe and realize the hiccups. Our consultants often find that companies are working historically – using processes that they have learned over the decades, even though there are rapidly changing tool sets available that can help (and are being overlooked).

What other findings from the survey stood out?

Cloud computing – the technology was envisioned as a threat 5-10 years ago. However, 55 percent of survey respondents perceived cloud computing as a true enabler today. This is an exciting new result! Cloud computing is also an enabler of artificial intelligence and big data because the cloud is needed to work in the immense and growing amount of data.

What are your thoughts on the future of digitization in pharma?

We often observe that new digital technologies – such as AI methodologies – are exciting because of what they seem to be. Instead of looking for a business case to use new digital technologies, companies should be looking at specific problems or business scenarios, and envisioning how sub-optimal processes could be improved in terms of quality, resources and quantity – in some cases, a carefully selected technology, such as AI, may be the solution but it depends on the problem. First, understand the problem; second, choose the most optimal automation tool that can help! There are a lot of compelling technologies out there. Our mission is to help manufacturers to better understand the options of the technology and to develop a strategy and roadmap for their businesses.

An Economic Infection

The coronavirus is likely to have an economic impact on the pharma industry. And highlights the need for analytics to help predict future "black swan" events and mitigate their effects

By George A. Chressanthis

There is certainly no shortage of news on the coronavirus contagion (officially, 2019-nCov) or the resulting disease COVID-19. But no one really knows what the future holds or what the long-term global effects will be. A big question is, will the coronavirus become a pandemic? Recent events suggest we are on the brink of such a declaration at the time of writing. If so, this will dramatically affect the global economy in ways previous pandemics have not, due to numerous economic system structural changes, such as China's emergence as a global economic superpower and the ease at which people can now travel around the world. Pandemics involving H1N1 (swine flu) from 2009-2010 are estimated to have caused global deaths between 284,500 and 575,400 people, based on statistical models (1). The high degree of viral contagiousness of H1N1 and its dissemination facilitated by the ease of modern global travel, similar to what we see today with the coronavirus, were key factors in causing the pandemic.

However, attempts to use previous virus outbreaks as a model for how the coronavirus will impact the global community (for example, the severe acute respiratory syndrome (SARS) outbreak and recovery in the 2002–2003 period) are likely misguided given differences in the transmission and dynamics of SARS versus the coronavirus. There is much we still do not know about the coronavirus, but it is certainly spreading well beyond China. Here, I look at the outbreak's possible economic effects on the global pharmaceutical industry – and why a sophisticated culture of "competing on analytics", as identified by Davenport and Harris (2), could help mitigate the

"The global economy shows signs of adverse effects from the expanding virus outbreak."

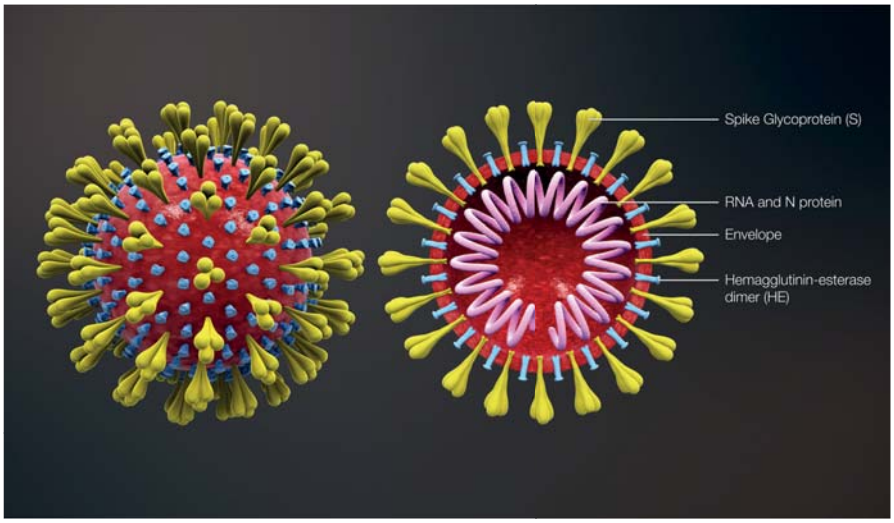
business impact when surprise events do occur.

In the news

The following list of news items (in chronological order) demonstrate the extent and speed at which this virus has already affected the global community:

1. The Dow Jones Industrial Average (DJIA) fell 1,031.61 points (3.56 percent) on February 24, 2020 because of expanding coronavirus concerns affecting the global economy (3). While history shows markets generally rebound quickly from such significant one-day pullbacks, the dramatic drop illustrates current uncertainty and fear around the coronavirus.
2. As of March 3, 2020, there were more than 95,500 confirmed cases, more than 2,900 deaths globally, and the countries hit by the virus had risen to 72, according to data from the WHO, with numbers rising daily The global economy shows signs of adverse effects from the expanding virus outbreak, with finance ministers and central bankers from the G-20 countries meeting in Riyadh, Saudi Arabia, on February 23, 2020 regarding the economic risks and what actions should be taken. The International Monetary Fund (IMF) has reduced China's annual growth projection to 5.6 percent – below the crucial 6 percent target rate which is important to Chinese leaders. Major producers around the world are also feeling the impact of supply chain disruptions from China on their own operations (5).
3. Travel bans instituted by other countries against the movement of people from China has affected commerce, culture, and Chinese students studying abroad.
4. US stocks with high exposure to China have significantly underperformed relative to broader market indices, showing the spillover effects that China has on the global economy (6).
5. Apple reported that the coronavirus will adversely affect the company meeting its revenue projections, illustrating the effect the virus has had on limiting production and demand inChina (7).
6. The virus is adversely affecting the economy in Japan through numerous channels (for example, tourism and production), along with the imposition of a sales tax increase, which now may put the world's third largest economy into recession (8, 9).
7. Volkswagen AG reported that some factories in China may remain closed due to the virus, illustrating the challenges companies are having in reopening operations (10). Some other factories are reopening, but under medical protocols that must be followed to limit the spread of the virus (11, 12).
8. Concerns have been expressed about the outbreak reaching a "turning point" since health

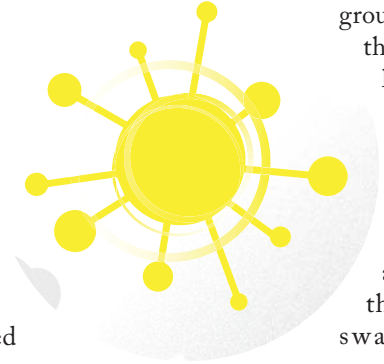
Cross-sectional model of a coronavirus



officials have been unable to contain the outbreak to China. Similar concerns have been expressed about what other countries, like the US, need to do to prevent the outbreak from hitting and spreading.

9. The virus is expected to affect US growth, according to a survey of economists, though the impact is predicted to be small (13). Federal Reserve Chairman Jerome Powell has warned of coronavirus risk to the US economy (14).
10. Kristalina Georgieva, Chief of the International Monetary Fund, spoke about the uncertain impact the virus would have on the global economy, which was sluggish (outside the US) even before the virus hit. She says the likely scenario is a V-shaped economic impact – a sharp decline followed by a rapid recovery (15). This prediction is based on the SARS impact, but ultimately, we don't know what the full extent of coronavirus will be, nor its economic effects. The role China plays in the global economy today is very different compared to the SARS outbreak of 2003. China's global GDP was 4 percent in 2003 and is 15 percent today (16).
11. The global supply chain has been adversely affected by the virus, with key commodity prices, such as oil, also taking a hit from the outbreak (17).
12. The virus has increased the price of many household goods in China, causing the inflation rate to be the highest in eight years (18). This trend in domestic prices can have spillover effects on the demand of other consumer goods, putting added downward pressure on global economic growth.

"The coronavirus decreases China's economic growth, which increases the risk of a global recession, which, in turn, decreases global aggregate demand for drugs."



The effect on pharma

The coronavirus contagion classifies as a "black swan" surprise, high-impact economic event, similar to other 21st century events that preceded it (for example, 9/11, Ebola, SARS, Trump's election, Brexit). The 2007-2009 recession and the 2009-2010 H1N1 pandemic could also likely classify as "black swan" events. Lastly, depending on China's response to this latest virus and its future policies to learn from and clamp down on commercial practices that provide the breeding ground for such outbreaks, the coronavirus may also likely not be the last one to materialize from China (19). However, using analytics it should be possible to predict and mitigate some of the effects of a "black swan" event like the coronavirus outbreak.

Right now, the potential effects from this latest event on the global pharmaceutical industry can be broken down into two possible pathways: demand and supply.

Demand

In terms of demand, the coronavirus directly decreases Chinese drug spending because the virus has caused a spike in domestic inflation, which

means the cost of consumer goods is rising, thus causing less demand for drug spending. China is the second largest drug market (behind the US) in the world, with 2018 spending at $137 billion (20). However, the vast majority of that spending affects domestic Chinese drug companies serving the China market. For branded, non-Chinese pharma companies, the share of global sales coming from China is still relatively small (21). The focus on and increase in specialty medicines (for example, in oncology) has been the driver of spending growth in developed markets. Specialty medicines now have an emerging market presence in China, although this too is still relatively small. Empirical analysis should be undertaken to understand how the decreases in China's economic growth and domestic spending caused by the outbreak will affect Chinese drug spending.

Another suggested effect stems from the reduction of pharma sales rep activity (to reduce personal contact and risk of disease spread), which could, in turn, reduce sales. There is a long and well-established body of pharma promotion-response modeling literature that shows how changes in sales rep activity affect sales. We also know from historical empirical industry evidence that new drug sales uptake in the early months of a launch is a strong predictor of long-term sales. If the outbreak persists, there could be longer-term implications for some product sales.

It is also possible that the coronavirus will increase the likelihood of a global recession via an economic shock to the system (22). The coronavirus decreases China's economic growth, which increases the risk of a global recession, which, in turn, decreases global aggregate demand for drugs. Also seen with the 2007-2009 recession, as governments faced declining tax revenues, higher entitlement spending for health programs, higher stimulus spending to reduce recessionary effects, higher budget deficits caused cuts in healthcare spending and branded drug demand through substitution to generics, tighter restrictions on prescribing and funding the utilization of patented drugs, and institution of price controls. The relationship between a recession and effects on drug demand has been recently noted in detail in The Medicine Maker (23). Also, importantly, these relationships can be empirically predicted and measured, along with the effects from pharma company countermeasures to mitigate recessionary effects on drug demand and revenue forecasts.

Supply

In terms of effects on the supply of pharmaceuticals, the coronavirus is disrupting the global supply chain of APIs developed in China and sent to other drug companies. Indian generic manufacturers are particularly dependent on raw materials from China – about 70 percent, according to one reference (24). The global implications of the supply chain disruptions are still unknown – companies are likely to buffer any effects through stockpiling and finding alternative supplies (21). However, confidence could be weakened in the longer-term stability of the Chinese supply chain system and cause companies to seek out alternative and more reliable sources of APIs, thus creating longer-term adverse effects for China. However, this could mean opportunities for other countries to fill in the gaps, as companies look beyond China to a more reliable source of materials. This redundancy might bring about longer-term beneficial effects in terms of companies being less reliant on China for APIs.

"A pandemic would exert significant pressure on global healthcare systems, affecting the supply of medical care for other condition."

Similarly, disruption caused by the coronavirus could also adversely affect the conduct of current clinical trials in China. A number of international pharmaceutical companies have heavily invested in China in the hopes of conducting less expensive clinical trials, obtaining access to large patient populations, and gaining access to an ever-growing Asian market. Again, companies may look to reduce future risks by geographically spreading the conduct of clinical trials so the system is less susceptible to a shock in any one country, like China. The length of the outbreak, how China responds to it, the degree to which China modernizes the drug and healthcare sector, and the confidence from investors that such shocks like the coronavirus will be minimized in the future, will determine the trajectory of future foreign drug company investments.

In addition, the testing of new experimental drugs, especially those developed from within the Chinese pharmaceutical industry, could be delayed, affecting China's efforts to supply drugs for its own market and globally deliver against the competition (25). If the outbreak continues, there could be significant effects in the longer-term for China to develop its own pharmaceutical industry and compete against global companies. If the outbreak becomes a pandemic, it may also shift R&D priority efforts toward addressing future virus pandemics, such as finding vaccines to handle future epidemics, and thus "crowd-out" investments on developing drugs for other conditions needed by society. Similarly, a pandemic would exert significant pressure on global healthcare systems, affecting the supply of medical care for other conditions, that could result in negative spillover effects on the utilization of drugs via demand-side effects.

Applying analytics to the black swan event

The outbreak of the coronavirus illustrates the inherent risks and uncertainties that are prevalent in the operation of a complex and global business, like the pharmaceutical industry. By their very nature, "black swan" events cannot be easily anticipated by business. However, it does not mean a pharma company is powerless to mitigate effects from a surprise incident. This latest contagion strongly demonstrates the need for pharma companies to invest in analytics. For example:

1. Engage in simulations and wargames to map out the possibility of surprise events and their potential effects. This means creating a culture of "blue-sky" or "possibility" thinking, with interdisciplinary teams and new processes to foster the creation of new ideas. A business should have the right incentives and culture for people to generate new ideas.
2. Attach risk coefficients and characterize the nature of uncertainty to future events that could bring significant harm to the company. This means having a "risk register" of potential events, attribute a likelihood of occurrence, and attach a degree of company impact to each event. Future events can then be prioritized for continued monitoring and contingency plans developed for possible implementation.
3. Create robust, empirical platforms to quickly detect and measure the existence and potential effects of unexpected events when they occur. Artificial intelligence and machine learning can be very useful here as identification and prediction mechanisms. Models can also look at the effect of mitigation efforts through business policies implemented if and when that future event does indeed occur. Creating a library of past empirical models applied and their usefulness can also be beneficial.
4. Translate empirical insights on the nature and extent of effects into actions based on empirically -driven business decisions. This means having a strong operations orientation and trust to execute plans based on analytics.
5. Develop a well-designed data architecture to supply your chosen analytical engines. This also means eliminating data silos commonly seen in pharma companies.
6. Senior leadership should promote and advocate an organization-wide culture of using analytics for all decision-making.

In my view, having detection systems that can quickly identify a problem, predict and measure the depth of effects, and then estimate the impact

of management control policies are crucial for the long-term success and stability of a pharma company. Putting proper empirical risk/uncertainty-mitigation controls in place, along with using analytics to gather insight on the effects of adverse global events, are essential to develop evidence-based countermeasures. And that's the only way to minimize impacts on business operations and, crucially, limit disruption to patients and healthcare systems from future black swan events.

George Chressanthis is Principal Scientist at Axtria. This article has been co-published with Axtria, a big data and analytics company, via their website, the Axtria Research Hub: https://bit.ly/3cJ07ul.

References

1. *Encyclopaedia Britannica, "Influenza pandemic (H1N1) of 2009," (2009). Available at https://bit.ly/2TepzyY.*
2. *T Davenport, J Harris, Competing on analytics: the new science of winning; Harvard Business School Press, Cambridge, MA, 2007.*
3. *CNBC, "Dow plunges 1,000 points on coronavirus fears, 3.5% drop is worst in two years," (2020). Available at https://cnb.cx/37X0UEB.*
4. *WHO, "Coronavirus disease 2019 (COVID-19) Situation Report – 43," (2020). Available at https://bit.ly/2xasBNs.*
5. *The Wall Street Journal, "Global economy shows strain as virus starts to take a toll," (February 24, A1, A6, 2020).*
6. *The Wall Street Journal, "Many stocks with China exposure miss out on market rally," (February 19, B13, 2020).*
7. *The Wall Street Journal, "Apple warns coronavirus to hit sales," (February 18, A1, A7, 2020.*
8. *The Wall Street Journal, "Sales tax and virus hit Japan economy," (February 18, A7, 2020).*
9. *The New York Times, "Coronavirus threatens to tip Japan's fragile economy into recession," (February 18, B2, 2020).*
10. *The Wall Street Journal, "Some VW factories stay closed," (February 18, B6, 2020).*
11. *The New York Times, "China's factories, badly hurt by a virus, struggle to reopen," (February 17, A1, A7, 2020).*
12. *The Wall Street Journal, "Businesses in China struggle to reopen," (February 11, A1, A7, 2020).*
13. *Fox Business, "Coronavirus likely to trim US growth," (2020). Available at https://fxn.ws/2Pqgu4V.*
14. *The New York Times, "Powell, warning of a possible virus fallout, is slammed again by Trump," (2020). Available at: https://nyti.ms/3a3jNaa.*
15. *Fox Business, "Coronavirus impact on world economy uncertain amid 'sluggish' growth: IMF chief," (2020). Available at https://fxn.ws/3a30g9Z.*
16. *The Wall Street Journal, "China's economic contagion," (February 4, A16, 2020).*
17. *The Wall Street Journal, "Virus shakes up global supply lines," (February 12, B13, 2020).*
18. *The Wall Street Journal, "Chinese inflation highest in eight years," (February 11, A7, 2020).*
19. *The Wall Street Journal, "China is the sick man of Asia," (February 4, A15, 2020).*
20. *IQVIA Institute for Human Data Science, "The global use of medicine in 2019 and outlook to 2023," (2019). Available at https://bit.ly/2HVtEmt.*
21. *FiercePharma, "How will coronavirus hit U.S. drugmakers? Depends what kind of drugmaker you are: Moody's," (2020). Available at https://bit.ly/3c90dez.*
22. *Fox Business, "What triggers an economic recession?" (2020). Available at Fox Business, published online 16 February 2020, available at https://fxn.ws/2T24clq.*
23. *G Chressanthis, "The Next Great Recession," The Medicine Maker, 61, 18-27 (2020). Available at https://bit.ly/2VnxSez and https://bit.ly/392NKHg.*
24. *CNN Business, "Drugmakers could be hit by the coronavirus. India is especially vulnerable," (2020). Available at https://cnn.it/2vg2B2o.*
25. *Reuters, "Coronavirus outbreak begins to disrupt booming China drug trials," (2020). Available at https://reut.rs/2wbDwWr.*

Making Pharmaceuticals

EXHIBITION & CONFERENCE

@makingpharma

Where The Pharmaceutical Industry Meets

GO!

2000+ Pharmaceutical Professionals

5 Industry Zones Within the Exhibition

200+ Exhibiting Companies

90+ Technical Sessions

28-29 April 2020

Ricoh Arena, Coventry, UK

Register at www.makingpharma.com

Free to attend

Profession

Your career
Your business
Your life

Onward in Oncology: Lessons Learned with Carlo Toniatti

Carlo Toniatti takes us on a journey from the clinic, to academia, to industry – where he spent over two decades developing anti-cancer drugs. Here, he shares the lessons learned along the way.

You can make a tremendous impact in drug development

The complexity of the oncology field is staggering, making it rather challenging but also fascinating to work in. Ultimately throughout my career, my focus has always been on working to improve the lives of patients. However, after completing my medical degree, I had to make a decision: do I pursue clinical practice or scientific research?

I initially began my career as a physician, despite having some inspirational oncology professors working in research. However, my interest in research remained strong during my time in the clinic, and I came to understand that I couldn't progress treatment options for oncology in the way I desired while continuing to work in clinical practice. I consequently realized, when working on transcription factors, that I wanted to develop drugs – and that has been the driving force throughout my career. As a physician, I was able to make a real impact on individual patients' lives through treatments that had already been developed - although this was only for a minority of cancer patients and the treatments often came at a cost of severe toxicity. However, I realized that as a research scientist, I could help more patients by contributing to the development of novel, more efficacious and better tolerated drugs against cancer types for which there were no effective therapies.

Specialization isn't always best

My path to industry is an interesting tale – and I owe a lot to a brilliant scientist named Riccardo Cortese. Riccardo was an Italian, from Naples like myself, who was leading the Gene Expression Programme (now the Genome Biology Unit) at the EMBL (European Molecular Biology Laboratory) site in Heidelberg. I was keen to join him so I went for an interview. It was the longest interview of my life – I was there for almost an entire day. In the end, he told me, "Carlo, I like you, but I can't hire you now." Naturally, I was disappointed. But it turned out he was in discussion with Merck Sharp & Dohme (MSD) to join as the director of a novel R&D site that was being built in Pomezia (Rome), Italy - he didn't want me to join and then have to deal with his departure soon afterwards. Eventually, he accepted an offer from MSD and then asked me to join him at the institute in Rome. The process taught me a lot about patience and compassion; and I have very fond memories of Riccardo Cortese, who passed away in 2017.

When I joined MSD, I really felt that it was my mission to make drugs. I started working broadly on cytokines and this led me to get involved in a project generating antagonists for interleukin 6, which multiple myelomas require for survival.

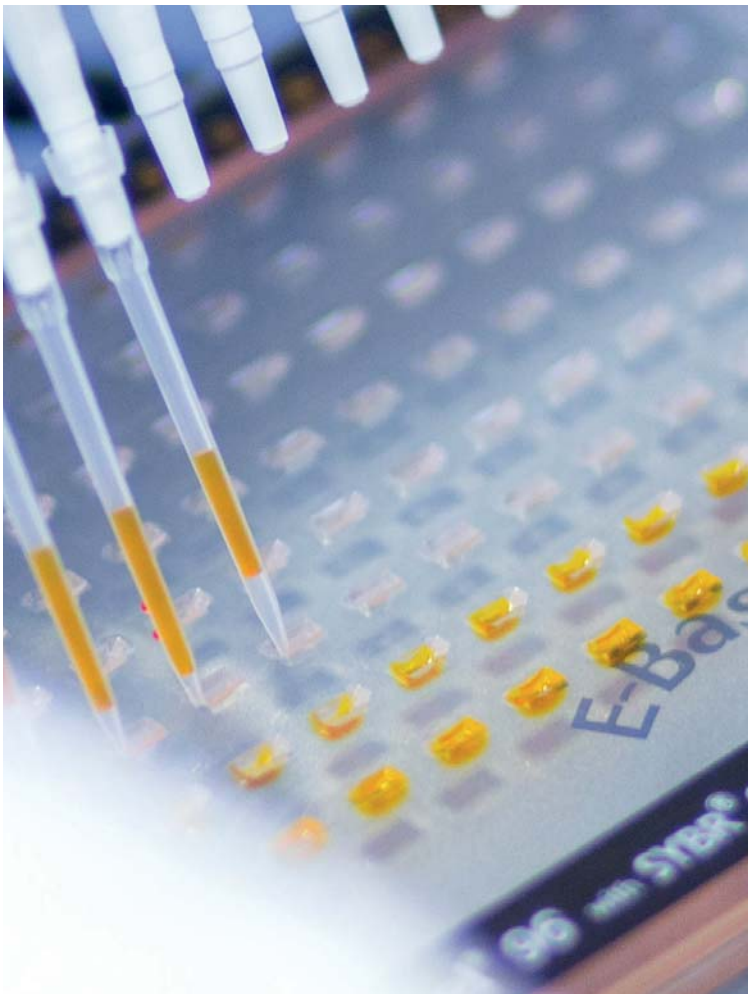
There's so much that you can learn within a big pharmaceutical company – things you can't really pick up anywhere else. Working in such a large organization means you see everything.

With all of the different therapeutic areas under one umbrella, if you work hard and find the right mentor and the right team, you can learn a great deal. I was lucky to find all of those things.

This period built the foundations for the rest of my career. In those days, you could start a project at the beginning

"There's so much that you can learn within a big pharmaceutical company – things you can't really pick up anywhere else."


E-Base
invitrogen



and see it, even lead it, through to the very end. You could go from target identification through to phase Ib-II of clinical development – covering the entire spectrum of drug discovery and development. Today, things are a little trickier because everything is specialized. Now, there will be a specialist in target identification, another in lead identification, one for lead optimization and another for IND enabling studies and so on. Personally, I'm grateful that I had the opportunity to see the wider perspective on these projects, and I feel it has served me well over the years.

"The culture of collaboration was fantastic, and you could tell everybody was passionate about the patients above anything else."

Academia and industry can complement each other

I started at MSD at the bottom rung of the ladder in 1990 and worked my way up to become director of the oncology site in 2007. MSD then made the strategic decision to shut down the site and I was offered the chance to relocate to Boston, where my family and I spent three years. I truly enjoyed my time there but when an opportunity arose at the esteemed MD Anderson Cancer Center, I couldn't turn it down – the challenge was irresistible!

The idea was to create an environment in which academics and those working in industry could work on drug discovery and development without spending time teaching, writing grants and applying for funds. I thought this was a great idea. Academics sometimes imagine that individuals working in industry only care about money, and that they don't understand how to analyze targets or run trials properly. On the flip side, people working in industry sometimes see academics as pie-in-the-sky thinkers who lack the rigour that is required to develop an approved therapy. Both of these visions are caricatures, but they do reveal the positive attributes that are unique to both groups. Drug development can be more fruitful when we combine the creativity of the academic world and the industry culture of clear milestones, precise goals and the focus on deliverables.

MD Anderson successfully created such an environment and I think it worked exceptionally well. We developed four drugs during my time at MD Anderson that are now in the clinic. The culture of collaboration was fantastic, and you could tell everybody was passionate about the patients above anything else.

Don't underestimate the importance of emotional intelligence

I left MD Anderson in 2018 and came back to Italy. The next step for me was to return to the old MSD site, which is now IRBM, an independent partner research organization. I always had a feeling that I might return, although I have a lot more responsibility now – previously I was Head of Oncology, but now I'm the Chief Scientific Officer. In this role, there is an important focus on managing people, as well as the research. You need a degree of emotional intelligence to do that well. It's vital to have everyone working together, concentrated on a common objective. Despite that, you also have to understand that people are different and have different perspectives. Some people want A and some want B - you have to be ready for that. It's important to remember that happy scientists are good scientists!

I enjoy working at IRBM because of the great culture we have here. We are really committed to a very high scientific standard and to "our" patients in the broader sense. These are the values that should drive people working in drug discovery and development. We work hard with the final goal of helping advance drugs to patients: solving issues,

delivering on tasks and advancing programs even when they are extremely challenging. Our partners frequently refer to us as "creative problem solvers", and I like this definition because these three simple words defines our strength. It's not just about mere execution but also hard work and commitment that is combined with creativity.

Remember who you serve

There's no doubt that the progress has been remarkable over the past three decades in oncology research – with the advent of targeted therapies and, more recently, immunotherapy – but that progress is measured through the positive results for patients. When it comes to rewarding good work and ethically conducting research, researchers must always keep in mind who they serve.

Serving patients should extend beyond clinical research, to ensure that public have the necessary knowledge to lead healthy lives. There is more we – both industry and more widely, healthcare – could be doing to prevent cancer through a greater awareness of healthy eating and exercise. At the same time, I think most people are aware of the link between smoking and lung cancer and have a generic notion that high intakes of red and processed meat can increase the risk of colorectal cancer. But how many people around the world are aware of the link between the use of tanning beds and melanoma incidence?

Appreciate progress without getting complacent

I've been lucky enough to see several drugs go from the discovery phase all the way through to phase III – and even become approved products. I've had conversations with many people over my career, talking about how their wives, husbands, children or parents are doing well after being treated with a drug we've helped develop – it really drives home why we do what we do. I do wish I could go back in time and treat patients with the drugs that are now available. Of course, that can't be done, but thinking about it gives me a perspective on the time spent in oncology and makes me appreciate how much better patient quality of life is when compared to 30 years ago. We're still only scratching the surface of what's possible with oncology treatment, and I'm excited to see how the field develops over the next 30 years.

Carlo Toniatti is Chief Science Officer at IRBM

Changing the Clinical Trials Game

We catch up with a new CEO and his goals for a clinical trials business

Stepping up into the role of a CEO comes with new challenges and responsibilities. Stuart Young has been working in the clinical trials business for more than ten years – and recently landed the CEO spot at Panthera Biopartners in the UK. We caught up with Young about his new role – and his thoughts on how clinical trials can do better. With increasing scrutiny growing over drug prices, pharma manufacturers are looking for ways to reduce costs across the board. One area where there is vast room for improvement and optimization is in the clinical trials process – with many believing that new data management and other modern technologies could help.

What is Panthera Biopartners?

We are an independent site management organization (SMO). Essentially, we use a world-class team of experts to run clinical trials on behalf of CROs and pharma companies, across multiple therapeutic areas.

What does your day-to-day job involve?

My real number one priority is meeting potential pharma and CRO clients and explaining the benefits of our offerings. But because Panthera is still early in its development, my current day job sometimes means "mucking in" on the basics, such as hiring new teams, analyzing each trial's feasibility or even deciding on internal build specifications (where the lights and sockets go!) for our new site, opening in North Manchester, UK, in March 2020.

My day-to-day role really is a case of doing whatever is necessary, but each building block helps us to grow from a solid foundation.

"Like any risk management decision, you work out what is critically important and then focus there."

Why did you choose to join Panthera?

It's a process. Like any risk management decision, you work out what is critically important and then focus there. For me, choosing a new job starts with me asking a question: "Do I want to work with the people involved?" In this case, the "people" were the founders – Ian Smith and John Lyon – and my answer was an emphatic yes!

After that, there were other factors to consider, such as the role and strategic vision, but a huge part for me was the opportunity to set an independent, modern, entrepreneurial and energetic culture – and build a business with those principles from the start. I see a real opportunity for an agile company like Panthera without any legacy issues or baggage. We can run with the latest advances in technology to offer a better product.

In any CEO role, what are the biggest challenges?

I expect different types of people will have different perspectives but, for me, it is controlling the urge to get involved in everything. Sometimes I stumble into something and realize that I just need to leave people to it – sometimes they have the good sense to tell me as well! I have a phenomenal team and they are tremendously well equipped to get most things done with or without my direct involvement. I like to surround myself with smart people who I trust, and that is what I have done. My job as a CEO is to keep everyone focused on our goals.

What are the biggest challenges right now in running clinical trials?

In this industry, patients are at the heart of what we do and we need to treat potential clinical trials patients like modern consumers. An airline who does not offer online booking and digital boarding passes would have failed 10 years ago, let alone in 2020! And yet, so much of our industry is still working to 20th century consumer standards. And that's not just the patient-facing aspects, but also internal technologies, such as paper source documentation and health data connectivity. Not long ago, I received a request from a customer asking what our corporate fax number was. I still have no idea what they intended to fax but it astounds me that these things are still required.

Additionally, I'd say personalized medicine is complicating the research world. Ultimately, the more stratifications needed, the more challenging it is to run the trial, as some cohorts will be easier than others. We are trending towards a point in time where each person will require individual medication, so testing the drugs involved is going to get incredibly challenging. Finding the individual biomarker for a therapy is already creating increased costs, particularly in oncology, and it's a trend that is likely to continue well into the future.

What are your goals for the company?

We have four basic stakeholders: patients, customers, employees and shareholders. Simply, I want all of those to feel that the company is the best option for them. For the business as a whole, my goals are to be at the forefront of the technological changes that are now changing the game of clinical trials, and to grow the business domestically and overseas. The business is very soundly capitalized and the response from the client community for a new independent SMO has been astoundingly positive to date, so I have no doubt that we have the backing to make the business a huge success.

What are your tips for others who want to move into a CEO role?

It's been a recent transition for me so I will probably be in a better place to answer this question sometime in the future! All I can say for now is that it is an all-consuming role so, if you can, take a break before you start and don't try to do everything yourself – delegate!

What's the most rewarding aspect of working in the clinical trials industry?

I'm sometimes amazed at the reasons people take part in a study. Of course, for some people it's a last resort, but for most people there is a very strong sense of altruism and wanting to ensure the next generation get better treatments.

We hear so much negative news about people being intolerant and unkind in the world today, but I can't think of anything more kind and thoughtful than taking part in clinical research.

Any other tips for running a successful business?

I cannot emphasize the importance of the right team – this extends throughout the whole company, regardless of position. We are upskilling all of our staff, with the medically trained staff working at the top of their licence and the opportunity for the admin team and clerical staff to become medical assistants or co-ordinators too, so that they can take blood and carry out the routine collection of samples, perform data entry, and all sorts of other value-add things that give us flexibility and avoid bottlenecks.

SPECIAL SERIES
Advanced Medicine

The Pharmaceutical Nomad

Sitting Down With... Miguel Forte, Chief Executive Officer at Bone Therapeutics, Belgium

Did you always want to work in pharma?
I always wanted to be involved with scientific challenges. I remember as a child being interested in biology – things like mammoths trapped in ice! – then later, biomedical science and eventually medicine. I saw medicine as a technical science that was also dynamic and relevant. Seeking this combination of science and dynamism is something that has shaped my career, as well as the desire to teach and to communicate.

How did you get into industry?
I did my PhD at the University of Birmingham, UK, on HIV, which was emerging at that time – in fact, we published a paper involving the first HIV patient in Portugal. From there, I was able to work on some of the first treatments for HIV. Getting these antivirals to work for HIV patients had a significant impact on me personally – I saw what innovation in drug development can do for real people.

I then left academia to work as a regulator for the EMA, which gave me the opportunity to look at some of these products from the other side – in terms of the risks and benefits. To develop a pharmaceutical product, there will always be an element of risk, but you have to take calculated risks to create value.

My experience of working on an innovative medicine, both in terms of immunology and patient benefit, made me think that going onto to develop products would be interesting.

How did you find the transition from academia?
Energizing! When I was appointed professor of a university in Portugal, I went to the leadership and proposed several changes. They told me my time would come to make changes, but that it was too soon! Taking the time to think, to brainstorm, to explore various potential avenues is important in a university – it's how new ideas are generated in early-stage research. But translating an idea into a product requires focused decision making – you have to dispense with what isn't necessary. I found industry to be a more natural fit and the transition was quite invigorating.

What are the most important lessons you've learned as a CEO?
Finding the right people is a huge part of success as a leader. I built a team from scratch when I was CEO at Zelluna; I was tasked with reorganizing the team as CEO of TxCell; and now I'm doing the same for Bone Therapeutics. You need to find talented people, put them in the right place, and then move together towards a shared vision. But you also have to know when it is time to end a project if it isn't going to work. Ending something can be painful, emotionally, as you may need to deconstruct and reorganize your team, but sometimes it is absolutely necessary for long-term success.

What excites you about your new role at Bone Therapeutics?
I was previously Chief Medical Officer for Bone, but moved on to lead and build another organization. I'm pleased to be able to return as CEO. Bone Therapeutics is a regenerative medicine company focused on orthopedics and bone diseases. And our core technology is an off-the-shelf allogeneic cell therapy platform, which turns undifferentiated stem cells from healthy donors into bone-forming cells. We have two assets going into middle and late-stage clinical development, with a market opportunity in sight. I'm excited by the prospect of being able to treat patients, not only in the clinic, but with an approved product. Plus, Bone is a big organization and this represents a significant challenge to set the vision, deliver on the clinical data, and also continue to foster innovation moving forward.

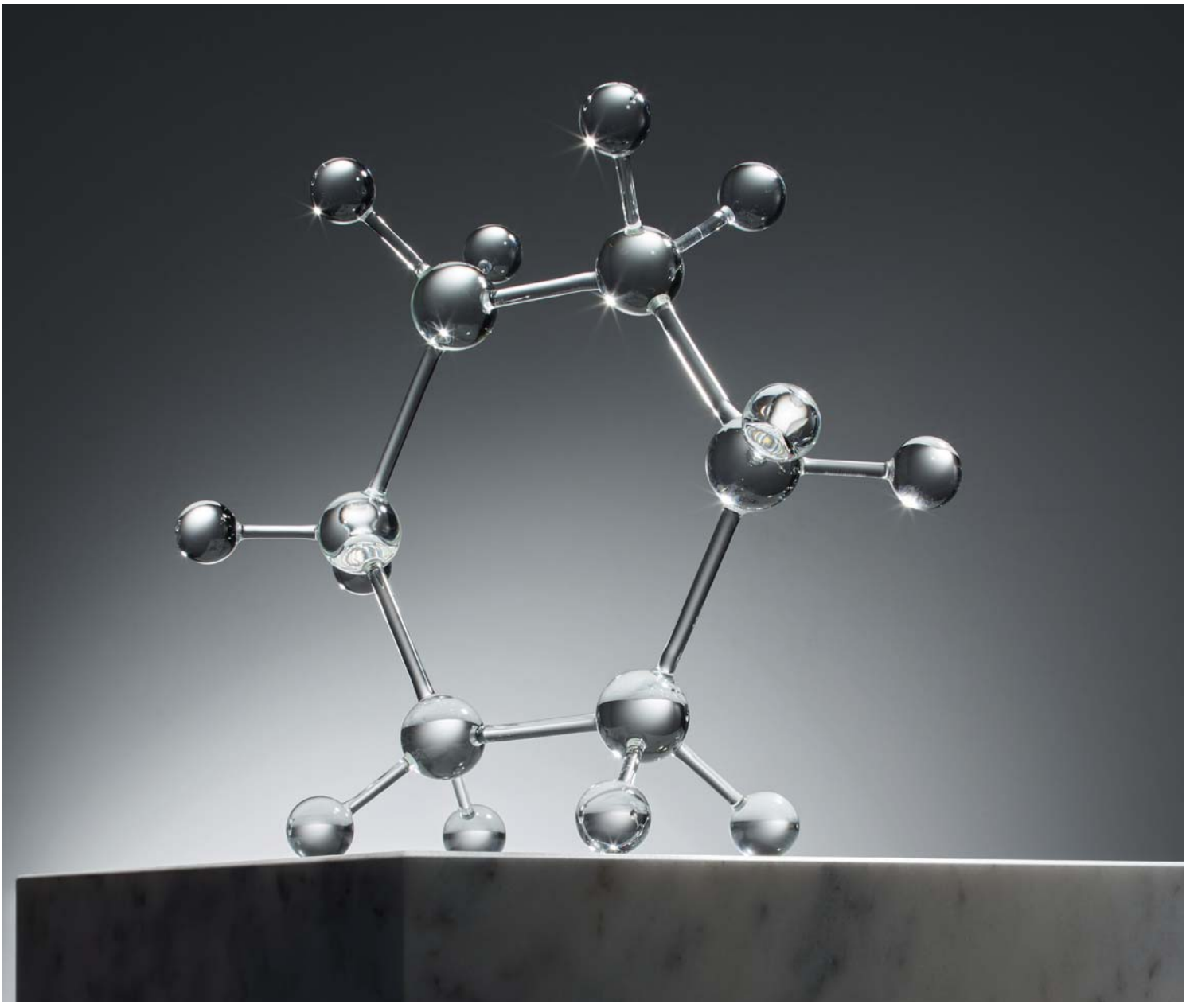
You're well known for commuting far and wide for work…
You could say that! I moved from Portugal to Belgium when I was at Bristol-Myers Squibb and the family settled there. We agreed that I could take a job somewhere else but they would stay. I've commuted to Dublin, the South of France, Norway… But it's not as though I'm sat in an office in another country week after week. The life of a pharma CEO is nomadic – flying to New York one week to talk to investors, Singapore the next for a conference, back to Europe to meet a client... It's just part of the job of a pharma CEO.

Recently, I was in San Francisco going from meeting to meeting on one of those electric scooters because we just couldn't get taxis. I had a real sense of purpose about what I was doing and when I got back to the office I felt energized speaking with the team about the possibilities. Although the trip was physically draining the sense of purpose and drive keeps me going.

Would you ever settle down?
My wife has given up asking me that question! I couldn't imagine working at a slower pace. But I'm sure there will be a time when I'll have to settle. I do love to teach, and help shape careers and watch people grow, so I could see myself shift emphasis towards that.

What about the cell and gene therapy industry as a whole… Is it living up to the hype?
I think new technologies tend to be overestimated in the short term and underestimated in the long term. We've had some big successes and that set up the expectation of being "the next big thing." The field is maturing now and showing resilience, but there are challenges to face.

What excites me most today is the opportunity to use cells as tools that can be engineered in multiple ways. Immunotherapy is offering significant value in terms of treating unmet needs, but we're also seeing the rise of regenerative approaches that will address morbidity, rather than mortality. And that's how the field will mature – by finding new solutions for different unmet medical needs.



DRUG DEVELOPMENT IS SCIENCE. CRAFTING SUCCESSFUL TREATMENTS IS ART.

Successful treatments with better outcomes for patients are built on science, superior formulation technologies and the art of drug design.

Catalent's passion and expertise guiding thousands of molecules into clinic is there to help you turn your science into reality. **Catalent, where science meets art.**

Catalent®

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