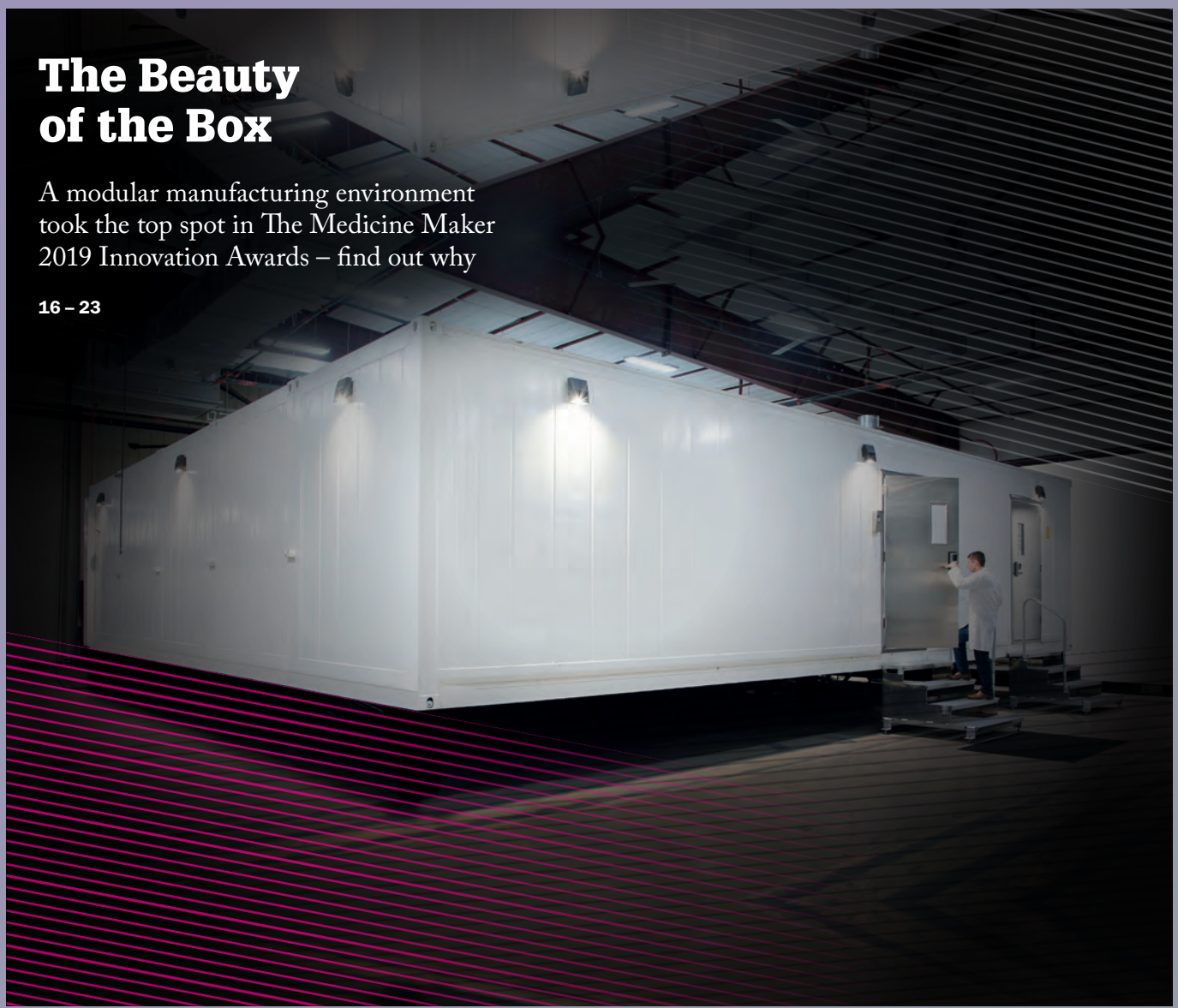
JULY/AUGUST 2020 # 67

the Medicine Maker™



The Beauty of the Box

A modular manufacturing environment took the top spot in The Medicine Maker 2019 Innovation Awards – find out why

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Facing the Challenge

Supply chains are under strain, but we must all continue to do our part

2020 began as a year with a focus on important trends in biopharmaceutical manufacturing: growing demand in "pharmerging" markets, cost pressures, more self-administered injectables, exciting new cancer therapies, and continued attention on cell and gene therapies. Then, in Q1, first in Asia, then in Europe and the Americas, we were suddenly confronted with an unprecedented challenge…

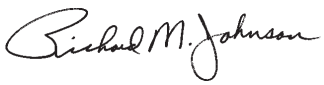
The COVID-19 pandemic has had a unique impact on our lives. Government health organizations have had to cope with a growing public health impact – simultaneously dealing with informing the public and governments about the risks, identifying the causative agent, developing effective diagnostics, providing guidance on treatment and protective measures, and accelerating the development of therapies and, eventually, a vaccine. And all of us have had to deal with quarantines, travel and economic disruption, and confusion over conflicting guidance from officials.

Despite all of these challenges, I am encouraged by the way the medical products industry has responded to the crisis. The rapid increase in demand for a wide range of products has put supply chains to the test. Personal protective equipment was one of the first areas where demand rapidly outpaced supply; masks, gloves, gowns, and sanitizers have been challenging to obtain, especially because the pandemic has affected workers in regions where these items are primarily manufactured. Diagnostic tools have had to be developed more quickly than usual, and there have also been increases in demand for both ventilators and the drugs needed to support mechanical ventilation.

At the same time, however, partnerships between clinicians and drug developers and the evaluation of numerous potential therapeutic avenues have proceeded with remarkable speed. Similarly, the development of vaccines has experienced a level of collaboration and development we've never seen before. Multiple candidates are under evaluation and we hope that the normal vaccine development time of several years will be shortened significantly.

We still have a long way to go. The pandemic is still growing and the challenges of balancing the resulting health and societal impacts will continue for some time. We must reevaluate our supply chain strategies to lessen our vulnerability to this type of disruption in the future. But I have confidence that all of us in the medical products industry will continue to do our part to get humanity through this crisis.

Richard M. Johnson
President & CEO, Parenteral Drug Association



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LABORATORY

On The Cover

Celebrating the grand winner of our 2019 Innovation Awards: Cytiva's KUBio box for viral vectors.

the Medicine Maker

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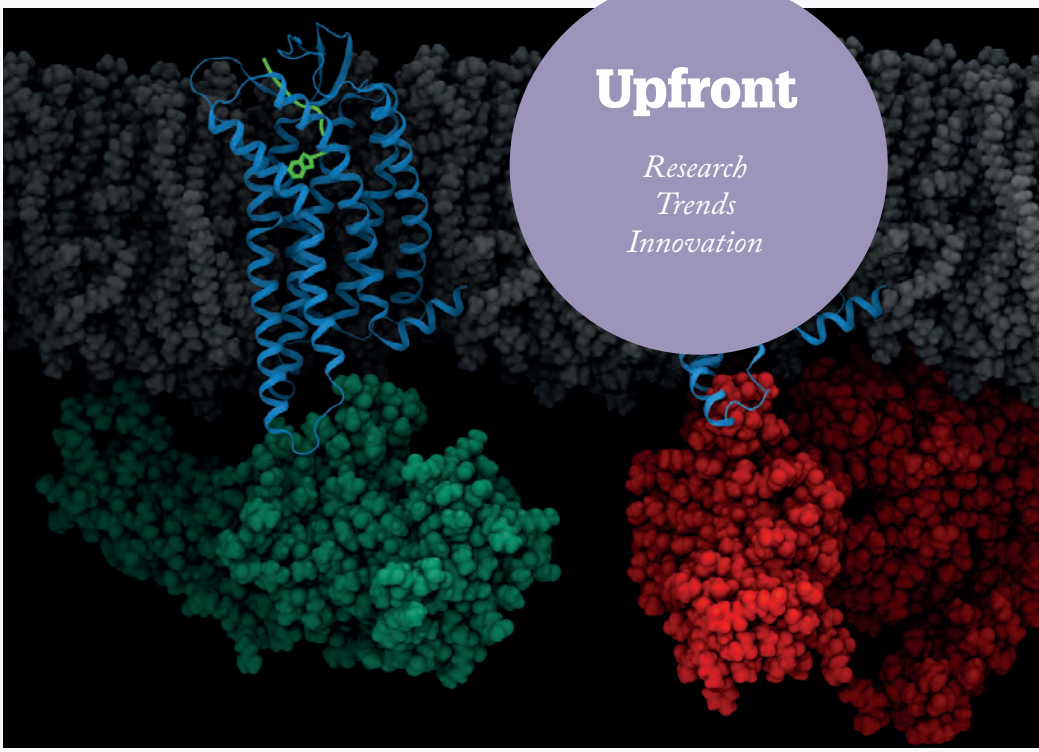


Upfront

Research
Trends
Innovation

The Good, The Bad, and The Side Effects

Can drugs be modified to eliminate their adverse effects?

Using simulations, researchers believe they can reduce the side effects of G protein–coupled receptor-targeting (GPCR-targeting) drugs (1). The aim is to design new drugs that alter the shape of these receptors in ways that activate beneficial signaling pathways but inhibit harmful signaling pathways.

"GPCRs represent the largest class of drug targets. In a phenomenon known as biased signaling, different drug molecules that bind to the same GPCR trigger distinct intracellular signaling pathways," says Carl-Mikael Suomivuori, a postdoctoral research fellow at Stanford University. "A drug can, therefore, bind to a GPCR and activate signaling pathways with beneficial effects for the patient while avoiding pathways that cause harmful side effects."

Investigating how this dual action could be exploited, Suomivuori and his colleagues ran molecular simulations of the angiotensin II type 1 receptor, a typical GPCR and a cardiovascular drug target. Their simulations revealed that, when bound to different drug molecules, the receptor adopted distinct conformations that made it more likely to interact with certain intracellular signaling proteins over others.

"Based on our simulations, we designed new drug molecules while predicting which signaling pathways they would activate. Testing these molecules in living cells confirmed that they worked," says Suomivuori. "We were able to design a molecule that, when bound to this receptor, not only inhibits harmful signaling that raises blood pressure, but also activates beneficial signaling that can improve the heart's ability to contract. Molecules of this kind promise to be safer and more effective cardiovascular drugs."

Though the team's research focused on GPCR-targeting drugs, they believe that their general approach of using simulations to come up with mechanistic hypotheses could be applied to other drug targets – allowing improved properties in a broad range of medicines.

Reference

1. *CM Suomivuori, "Molecular mechanism of biased signaling in a prototypical G protein–coupled receptor," Science, 367, 881, (2020).*

INFOGRAPHIC

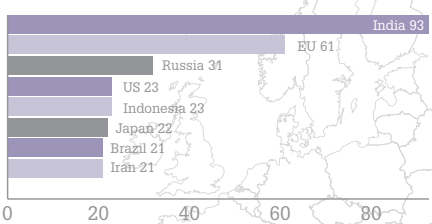
Guiding Biosimilars Regulation

A WHO survey explores regulatory landscape for biosimilars and how guidelines have contributed

World's first approved biosimilar: Omnitrope – approved in the EU in 2006

Dominant product class for biosimilar development: mAbs
In some countries, locally produced biosimilars may become dominant products in the future

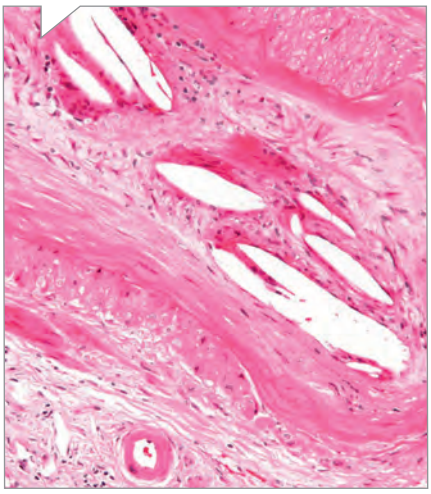
Regions with the highest numbers of biosimilars approvals*



ADVANCED MEDICINE IN BRIEF

CAR T for aging, gene therapy for heart disease, and the launch of a two-million euro gene therapy

- Could gene therapy cut cholesterol? Verve Therapeutics researchers knocked out two cholesterol-associated genes, PCSK9 and ANGPTL3, in cynomolgus monkeys, resulting in up to a 60 and 65 percent reduction in LDL cholesterol and triglycerides respectively. Joseph Wu of Stanford University said the degree of LDL and triglyceride lowering "looks good compared to statins," and Michael Davidson, University of Chicago, went as far as saying, "This could be the cure for heart disease."
- Novartis is set to launch its spinal muscular atrophy gene therapy Zolgensma in the EU, starting with Germany where the drug will be priced at €1.945. The company says it is also in discussion with the UK. The European Commission granted a conditional marketing authorization for the drug at the end of June, covering children and babies weighing up to 21 kg with the most severe form of the muscle-wasting disease, spinal muscular atrophy.



- Remestemcel-L, Mesoblast's mesenchymal stem cell therapy for inflammatory diseases, improves lung function and exercise capacity in people with chronic obstructive pulmonary disease and a high degree of inflammation, according to data presented at the 2020 International Society for Cell & Gene Therapy's annual meeting.
- Sloan Kettering Institute researchers use "uPAR-specific CAR T cells" to "efficiently ablate senescent cells in vitro and in vivo," reversing some surrogates of aging in mice, such as liver fibrosis. However, the researchers did not report data on whether the CAR T cells actually extended the lives of mice.

Biosimilars' 2020 Breakthrough?

The FDA approves its first biosimilar of 2020

The FDA has approved Pfizer's Nyvepria (pegfilgrastim-apgf), a biosimilar of Amgen's oncology supportive care drug, Neulasta. The approval is the FDA's fourth for a biosimilar pegfilgrastim – and the first biosimilar approval for 2020. The drug, which is approved to prevent infection in patients receiving myelosuppressive anticancer drugs, has also been submitted to the EMA for review.

Although Pfizer plans to market the drug in the US later this year, Nyvepria is also the subject of ongoing litigation. Earlier this year, Amgen announced it was suing Pfizer over allegations that, when developing Nyvepria, Pfizer's Hospira unit infringed on a Neulasta patent focusing on protein purification. Originally scheduled for June 2020, the trial has been postponed until May 2021. All previous biosimilar pegfilgrastim drugs have also faced lawsuits from Amgen.

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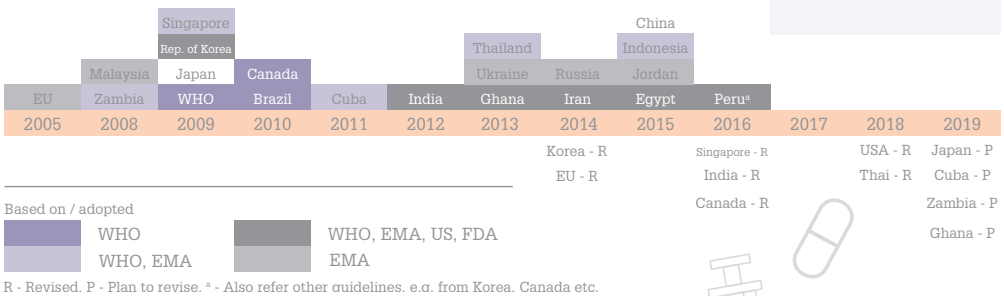
1. *Pfizer, "FDA Approves Pfizer's Oncology Supportive Care Biosimilar, Nyvepria (Pegfilgrastim-apgf)" (2020). Available at https://bit.ly/2AbOY6T.*
2. *FDANews, "Amgen Sues Pfizer, Hospira in Neulasta Patent Dispute" (2020). Available at https://bit.ly/2VqrIcY.*

Timeline of guidelines from WHO and 21 regulatory authorities



R - Revised. P - Plan to revise. [a] - Also refer other guidelines. e.g. from Korea. Canada etc.

Sources: N-N Kang, R Thorpe, I Knezevic, "The regulatory landscape of biosimilars: WHO efforts and progress made from 2009 to 2019," Biologicals, 65, 1-9 (2020).

The Natural Drug Factory

Exploring how microbe mega-enzymes synthesize critical chemical compounds – and drugs

Researchers are shining a new light on how nonribosomal peptide synthetases (NRPS) work (1). Known for their ability to make "natural product peptides" – small, but potent chemical compounds – these multienzyme nanomachines have been used to develop a variety of drugs, including immunosuppressants and antibacterials.

"NRPS act as machines, with many moving parts and reaction centers that all work together," says Martin Schmeing, Associate Professor in the Department of Biochemistry at McGill University. "They follow an elegant sort of logic in which a subsection called a module facilitates reactions that add building blocks to a growing chemical. The enzyme then passes the (now bigger) chemical to the next module, where the next building block is added, and so on."

But the configuration of these modules has remained elusive – until now. Using ultra-intense X-ray beams, Schmeing and his colleagues were able to visualize the NRPS' mechanism of action, by studying an NRPS called depsipeptide synthetase "We found that the modules converted keto acids into building blocks that can be added to peptide drugs," says Schmeing. "This helps us understand how NRPS use so many building blocks to make different compounds and therapeutics. This understanding will help us build new therapeutics from new combinations of building blocks." The researchers believe the module subsection unexpectedly acquired portions of another enzyme through evolution, enabling it to use different building blocks in chemical synthesis.

This knowledge should help us to begin producing more potent drugs with desired properties using NRPS. But Schmeing points out that there is still much to learn before we can fully understand these nanomachines. "In our study, there was a small but important section of the module that was not visible in some of our experiments," he says. "We are aiming to visualize this in the future and evaluate its contributions to NRPS function."

Reference

1. *DA Alonzo et al., "Structural basis of keto acid utilization in nonribosomal depsipeptide synthesis", Nature Chemical Biology, 16, 493 (2020).*

Learning from Past Impurities

EMA reviews lessons learned from nitrosamine impurities

Following a "lessons learned" exercise, the European medicines regulatory network has published recommendations to reduce the risk of drug impurities. The recommendations clarify companies' roles and responsibilities when it comes to controlling, detecting, managing, and communicating impurities.

In mid-2018, nitrosamines present in some sartan medicines led to recalls and other regulatory measures. The impurities came from the use of dimethylformamide and sodium nitrite, which, in the presence of an acid, led to the formation of N-nitrosamines during API manufacture. EMA also identified the potential for contamination from other sources. Although nitrosamines were not previously recognized as impurities in sartan medicines, animal studies show that they are a probable human carcinogen. As a direct result, the "lessons learned" exercise was launched to explore how unexpected impurities could be prevented and, if they do occur, how to manage them in the future.

The recommendations are available on the EMA website: www.ema.europa.eu

IMAGE OF THE MONTH

Furnace Refurbishment

Bormioli Pharma has completed the refurbishment of its glass furnace in San Vito al Tagliamento. The company has implemented new technology and Industry 4.0 concepts to improve production efficiency and reduce its carbon footprint.

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QUOTE of the month

"The devastating human cost of the COVID-19 crisis drove everyone involved in bringing new diagnostics, vaccines and treatments to patients to adopt a mindset of simplifying and accelerating procedures. The 'new normal' in regulatory terms should embrace this attitude, aiming at decreasing complexity while ensuring the quality, safety and efficacy of the medicines for patients who need them."

Nathalie Moll, Director General of EFPIA: https://bit.ly/2NFzbQP

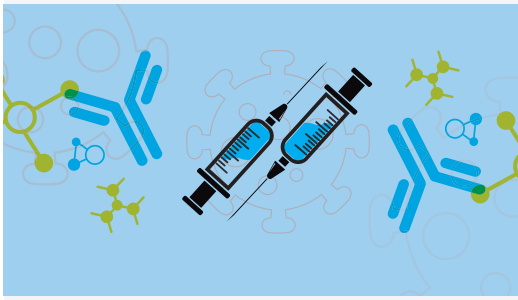
For a Better Future

A private-public sector alliance supports the development of immunization programs around the world

Gavi's latest replenishment conference, The Global Vaccine Summit, helped raise $8.8 billion to improve international immunization programs. The event, which marked the alliance's 20th anniversary, brought together representatives from 52 countries who committed to ensuring that 300 million children across the world have access to essential vaccines despite the pandemic's impact on supply chains and logistics.

Gavi also published a manifesto that outlines the actions its donors and partners have taken to address the problem. Alongside immunization programs, companies have developed manufacturing and supply solutions that make it easier to get vaccines to hard-to-reach places. For example, Pfizer has worked with Gavi partners Zipline and the Bill and Melinda Gates Foundation to establish a medical drone delivery system in Ghana.

The manifesto can be found at https://bit.ly/37HhpG7.



In My View

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

The Pandemic Diaries

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

Tony O'Sullivan, Chief Commercial Officer at ChargePoint Technology

As a population, we are currently learning how to function during a pandemic. Everyone is claiming "business as usual" – but can this really be the case when there are still restrictions on global travel and social distancing? Actually, for pharma, the answer is (more or less) "yes." Although delays in receiving APIs and raw materials are one of our biggest challenges, the industry is proving that it has solid business continuity plans in place – and they are working. We need to ensure that the industry continues to come together to help slow the pandemic, whether through direct industry partnerships or via local and regional networks. Every company in the pharmaceutical supply chain must play their own part to keep the wheels turning in such a vital industry.

With the loss of most big industry events, many companies – including my own – are exercising creativity in terms of finding new ways to meet those we would normally network with face to face – for instance, virtual meetings. Suppliers and vendors are also taking this approach on board, with product demos conducted virtually from living rooms and home offices all over the world. Those who are best set up to support their customers remotely will be the ones who thrive in the current situation.

By Will Downie, CEO at Vectura

For many years, I spent a good proportion of my working life travelling – constantly flying around the world. But since lockdown, like so many others, I've been spending every day of the working week in my home office on video conference calls with customers, investors and our internal team. In my new role, and at the beginning of lockdown, I found it frustrating not to be face to face with my colleagues – but what has surprised me most during the pandemic is how quickly many companies – including my own – have adapted to these difficult circumstances. We've embraced technology to keep us all connected. We've delivered for our customers. And we've stayed flexible, supporting one another through many challenges.

Why have we adapted so well? To me, the answer is leadership; not just at the top of the company, but as the spine that runs through it. Leaders have had to be more visible (virtually and, where possible, on the ground) than ever before, as well as becoming better communicators and reassuring decision-makers. They have also had to work with real empathy to manage uncharted situations.

This pandemic has held up a mirror to leaders in every organization and I am proud to say that what I have experienced gives me confidence that we will emerge from this crisis as an stronger and more resilient company.

By Andy Chaloner, CEO of Stream Bio, and Stephane Argivier, CEO of MIP Diagnostics

The speed and severity of this pandemic has vastly changed business and research priorities for many biotechnology companies and sparked many new partnerships – including one between our two companies. We'd discussed the possibilities of our companies working together in the past, but it was the pandemic that finally cemented the relationship – one we hope will continue long after the pandemic ends!

Our current collaboration focuses on diagnostics. There is a huge need to improve COVID-19 diagnosis times and laboratory testing capacity. To this end, the industry needs appropriate reagents. We'll be using our Conjugated Polymer Nanoparticles (CPNs) and high-affinity molecular imprinted polymers (MIPs) to create adaptable detection reagents for various diagnostic assays – including ELISA-format assays and lateral flow. We hope to reduce diagnosis times to just 10 minutes.

As the pandemic progresses, it is essential that we have robust diagnostic development and manufacturing infrastructure in place to meet future demands. Syntehtic CPN and MIP development rimes are much shorter than traditional reagents, so if new mutations were to arise in the virus spike protein, diagnostic reagents could be adapted and scaled quickly to target novel variants.

By Edward Haeggström, CEO of Nanoform

My area of expertise lies in nanotechnology, and I've been delighted to see the field contributing to the fight against COVID-19. The race is on to find an effective treatment and it's critical that we consider both established and novel approaches. New technologies, including nanotechnology, are playing a huge role in the quest for therapies. This is because the SARS-CoV-2 virus acts at the nanoscale and successful treatments may require an approach that works within this size range. One current avenue of research is the development of drug particles with a similar size to the virus that may be engineered to attach to it and disrupt its structure. Scientists at the US Centers for Disease Control and Prevention are already working on developing new medicines that act in the nanoscale size range, along with sprays to disable the pathogen before it reaches the body.

Nanotechnology also plays a critical role in the development of a vaccine. For example, mRNAs in combination with lipid nanoparticles are being investigated, based on previous studies involving SARS-CoV and MERS-CoV. In addition, my university lab has been developing drug-laden nanofiber constructs to help wound healing for several years; the same technology could potentially be used to create next-generation face masks for COVID-19 management. Though there is a great amount of work still to be done, we are encouraged by the collaborative spirit fostered in the past few months and the important contributions from the nanoparticle engineering community so far.

Getting a Handle on High Potency

We need to optimize and then accelerate HPAPI drug product development

By Alyn McNaughton, Technical Director at Lonza Pharma, Biotech & Nutrition

New treatments under development are increasingly specialized, selective, and potent. Highly potent API (HPAPI) compounds are designed to be more effective at the site of therapy while minimizing adverse events. The manufacture of HPAPIs, however, comes with significant challenges. By their very nature, HPAPIs are often toxic to the workers who manufacture them, necessitating a high degree of controlled handling. Additionally, the low concentrations typically required for administration make accurate dosing more challenging – each dose may only contain the equivalent of a single particle of the API as supplied from the manufacturing process. Furthermore, these new molecules

are often poorly soluble to insoluble, causing bioavailability issues.

Microdosing can help advance some HPAPI products. This automated process uses specialized, highly precise weighing equipment to dose unformulated API powder into hard capsule shells. It allows for rapid product development in a solid oral dosage form typically preferred by patients. For HPAPI drug products, the dosing can be performed in isolator technology, which is sufficient for most molecules that require only small quantities of material to be handled.

But many HPAPIs have properties that prevent the use of microdosing. They may be sticky, semi-solid, liquid, too light, or "fluffy." The powder may not flow, or API particle size/shape may be inconsistent. In some cases, compounds may be so potent that the safe containment level cannot be readily achieved or the dosage itself may be below the weighable range of microdosing.

The ability to incorporate powders into a liquid, either as a suspension or a solution, can negate many of the properties listed above. In my view, liquid-fill hard capsules (LFHCs) offer an effective formulation approach for accurate and consistent low-dose applications, as well as a safe and effective processing approach for HPAPIs.

LFHC formulations are composed of either room-temperature liquids or thermo-softening materials – the latter of which are manufactured as a molten liquid at temperatures up to 65°C. Sticky, semi-solid, and liquid HPAPIs are often miscible in liquid excipients, meaning the materials can usually form a homogenous mixture. Light, "fluffy" powders and inconsistently shaped APIs, if less miscible, can be homogeneously suspended in liquid excipients, which means they can be managed more generically. HPAPI particle size and shape variability can cause challenges when manufacturing a conventional dosage form, because powder flow properties may prevent development of a homogenous powder mix. Incorporating the API as a suspension in a lipidic excipient can help address those challenges. High-shear mixing is routine for suspensions in liquid and allows sufficient homogenization to overcome most particulate dispersion issues – and can even break down agglomerates, generally without reducing primary particle size. A thixotropic agent can be added to gel the system and prevent de-homogenization over time. For liquids, this can be accommodated within a generic, single-step mixing process, obviating the additional development time required for conventional dosage forms.

At very low doses – often needed for HPAPI products – producing a homogeneous mix to facilitate an accurate unit dose product is challenging. The greater mixing potential of powder in liquids, relative to mixing powders, can support generating some formulations as suspensions (where a powder mix would often be inhomogeneous). For a liquid suspension formulation to provide accurate low doses, the process still requires the API's primary particle size to be small enough to ensure a sufficient number of particles in each unit dose – so that an even distribution of particles results in an accurate dose. For larger particulates, this can be achieved using a bead mill to reduce the particle size of an insoluble powder suspension directly in the liquid manufacturing process. In this process, particle size reduction happens as part of routine mixing and does not require a separate process.

The ideal situation is to generate a solution that ensures the exact dosage (no matter how low) is determined only by the filling accuracy into individual capsules. Specialized liquid-filling machines provide a very high level of accuracy and precision for this process.

An overall benefit of using LFHCs for HPAPI product development is their relatively straightforward manufacturing process compared with other technologies capable of producing low-dose product profiles, such as wet granulation tableting. Liquid hard capsule formulations only require three processes – mix, fill, and seal – whereas wet granulation tableting requires seven: dry blending, wet mass preparation, sieving, drying, screening, granulation, and tablet compression. Powder stages during the process also require containment for airborne particulates, adding another step. Especially where a solution has been achieved, liquid formulations can also help accelerate the development process from feasibility studies to commercialization; the scale-up of the bulk formulation mixture to meet commercial demand only requires dissolution of API in excipients to ensure an equivalent process.

The risks of handling powder HPAPIs during LFHC development, from dispensing until incorporation into the liquid, can be mitigated using routine isolator and closed powder transfer technology throughout the development stages. For the remaining processing steps, the powder is solubilized or entrained into the liquid, so operators are safe to continue working with significantly less engineering controls.

Finally, many new HPAPIs are also lipophilic and suffer from poor solubility and bioavailability. They are often not therapeutic enough to meet their clinical targets. For these drugs, developers can use liquid and lipid technologies to emulsify HPAPI molecules, enhancing solubility without an additional enabling technology.

In my view, LFHCs offer many flexible benefits to today's candidate HPAPI molecules. The market value from existing and new HPAPI product launches is expected to double between 2018 and 2025, from around $18 billion to $35 billion (1). With 25 percent of all drug products – and around 70 percent of drug products in the oncology sector (2) – requiring some type of specialized

handling, the need to develop these products quickly and safely has never been greater. HPAPI formulations are challenging to work with, but solutions like LFHCs can offer an effective path forward.

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Greening the Pharma Toolbox

Green manufacturing was often not a consideration when most pharma processes were initially developed. But sustainability deserves greater recognition today – and the pressure is rising.

By Martin Hayes, Biotechnology Lead at Johnson Matthey

Process development is a lengthy, complicated, and expensive process, so there is always a desire for technologies that facilitate the development of more cost-effective and robust processes. Many pharma processes were developed in an era when waste generation and sustainability were not key considerations. Today, as the global market shifts towards realizing a greener economy, there is increasing pressure on the pharma manufacturers to redesign manufacturing processes to make them more environmentally friendly – and this can also translate to a more competitive edge; less waste means higher efficiency. Fortunately, there are ample opportunities for pharma companies to transition to greener chemical processes.

Traditional pharmaceutical manufacturing uses a "take-make-dispose" model but, in my view, we should be moving towards a sustainable, circular process that is regenerative by design, where waste is transformed into value. We need to signpost the cost savings of replacing fossil resources with renewable raw materials. There are many modern biochemical technologies that can help pharma to make the switch. For example, there is a new suite of bio-based technologies that could help the industry develop complex, high-value molecules with carbon sources, mainly from sugars and fats. In these processes, the carbon used is not fossil-based, but from renewable sources that can be found in traditional – and practically inexhaustible – waste streams.

Biocatalysis, in particular, is appealing for several reasons. Enzyme-based catalysts meet the demands for safe and sustainable industrial processes. Furthermore, because enzymes rely on specificity they can synthesize complex structures with high levels of regio-, chemo-, and stereo-selectivity. And they can give chemists access to highly selective transformations, including chiral amines, alcohols, or carboxylic acid derivatives, with minimal by-product formation.

Biocatalysts do come with specific challenges though. Enzymes are commonly denatured by organic solvents, so water is the predominant solvent for enzyme-catalyzed reactions. Due to its high-boiling point, separating the desired product from water can add undesired cost to a process. Additionally, during the drug development process, manufacturers aim to define the optimum route as early as possible. Though off-the-shelf enzymes are commercially available, there are limited numbers and limited reaction class coverage. As such, an initially identified enzyme rarely has all the properties required for a viable process, meaning further protein engineering is almost always required.

Recent advances in molecular biology, protein engineering, and automation, however, have improved our ability to discover and engineer novel enzyme classes to build complex molecules. For example, nitroreductases have been developed to reduce nitroaromatics to their corresponding amines. Furthermore, modern low-cost DNA synthesis has provided access to new biocatalysts at industrially relevant timescales. These advances aid in the development of cascade biocatalysis, where multiple steps can be performed in a single pot or cell, increasing synthetic efficiency, eliminating steps, and reducing waste generation.

To ensure a more sustainable future for the pharmaceutical industry, we must continue to develop and implement biotechnological processes. I believe ongoing advances in bioinformatics and protein engineering will provide access to new chemistries at unprecedented speed. As an industry, we are just beginning to take full advantage of these biotechnological tools. To overcome future challenges, collaboration across the industry is crucial. Pulling together expertise and insights from biologists, chemists, bioengineers, process engineers, and material scientists will allow us to economically and efficiently develop the biotechnologies of the future.

Breaking Through the Barrier

How nanotechnology offers new potential for delivering drugs through the skin

By Dave Cook, Chief Scientific Officer at Blueberry Therapeutics

As the largest organ, our skin typically accounts for around 10 percent of our body mass. In terms of drug administration, however, it remains a relatively unexplored frontier. The skin has evolved to be an excellent natural biological barrier, making it challenging for drugs to penetrate it in sufficient quantities to reach therapeutic concentrations (1).

The skin has a multi-layered composition, so the capacity of a drug to enter and pass through depends on its ability to penetrate both the hydrophobic and hydrophilic layers of the skin. Drugs that are too hydrophilic are unable to pass into the outer layers (the stratum corneum), whilst very lipophilic drugs will be retained in the lipids of the stratum corneum and will not pass into the more aqueous epidermis, limiting permeation. Skin permeability may also be affected by a large number of physiological factors, including the anatomical site, age, ethnicity, gender, and underlying skin disorders (2, 3, 4). Skin is not a homogenous unchanging barrier, which means therapies designed to use the skin as a site of delivery need to be tailored appropriately to be effective.

Despite the challenges, the pharmaceutical industry should not be so hasty in writing off skin-based drug delivery! Topical administration represents a non-invasive, painless and convenient alternative to injection and avoids the first-pass liver metabolism typically encountered by oral drug delivery. Transdermal delivery into subcutaneous tissues and then into the body also has the potential to deliver steady and sustained drug levels over prolonged time periods, thereby reducing side effects associated with the peaks and troughs in drug plasma concentrations that are common with more acute dosing routes, including oral administration (5).

Clearly, the skin itself is the site of many common diseases and disorders, such as fungal infections, psoriasis, skin cancers, dermatitis, and acne. Here, direct (topical) treatment would logically be the preferred route of administration, as it targets the site of disease directly whilst limiting any unwanted systemic exposure. Indeed, formulations based on nanotechnology should allow the usage of lower doses – as well as shorter treatment times and less frequent applications.

Nanotechnologies can help tackle many of the challenges presented by skin delivery. Nanocapsules, nanoparticles and liposomes are all viable options (6) – and all of these approaches are characterized as "nanoformulations." Nanocapsules consist of a lipophilic solid or liquid core enclosing a hydrophilic drug surrounded by a polymeric coating structure. Nanoparticles, on the other hand, are formed using synthetic polymers with high hydrogen binding potential, mixed with the therapeutic molecules or cargo (peptides, nucleic acids, or small molecules), which then rapidly assemble or package into nanoparticles. Finally, liposomes consist of an aqueous center where drugs are surrounded by a hydrophobic membrane in the form of a lipid bilayer.

In my view, novel delivery systems that can safely and effectively deliver drugs through the skin have the potential to replace conventional therapies. Right now, we're in a period of evolution rather than a revolution – dermatological conditions are an obvious place to start – but imagine a future when nanoformulations are able to transport a variety of molecules, such as antibodies and proteins, through the skin… When that happens, I believe transdermal will become the go-to mode of drug delivery.

"Despite the challenges, the pharmaceutical industry should not be so hasty in writing off skin-based drug delivery!"

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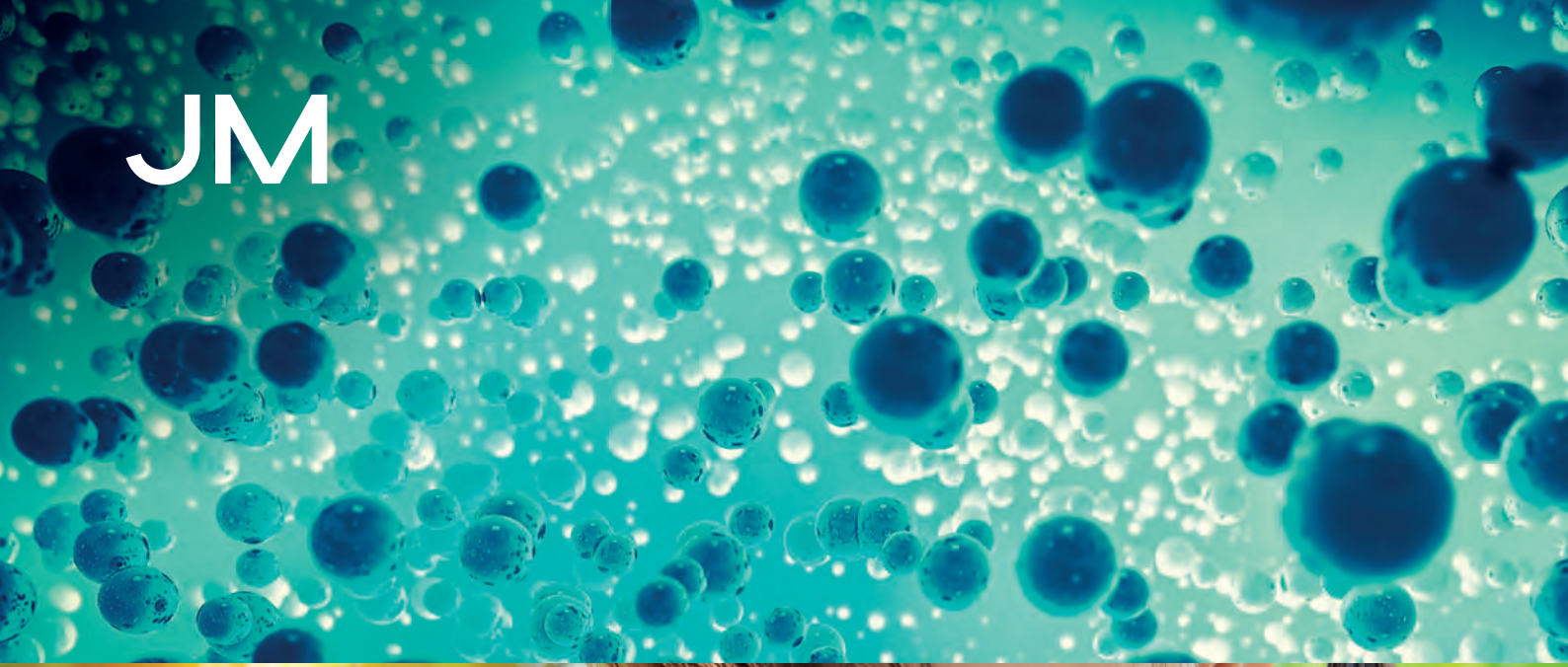

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THE BEAUTY OF THE BOX

CYTIVA'S KUBIO BOX MODULAR ENVIRONMENT FOR VIRAL VECTORS TOOK THE TOP SPOT IN THE MEDICINE MAKER 2019 INNOVATION AWARDS. HERE, WE EXPLORE WHY THE INDUSTRY IS SO EXCITED ABOUT MODULAR BIOPROCESSING CAPABILITIES.

It has often been said that pharma is slow to change, but when it comes to biologics that notion does not hold true. Bioprocessing is no longer about just monoclonal antibodies – cell and gene therapies have emerged as one of the hottest topics in the industry. The COVID-19 pandemic is also driving many companies to evaluate new approaches to vaccine manufacture. Bioprocessing is becoming more diverse and companies require flexible facilities that allow them to adapt to changing demands for different products.

Cytiva developed its KUBio facility to help companies quickly deploy new manufacturing capabilities. A KUBio facility is made up of modular units, allowing for design flexibility – and also offering the capability for companies to expand further as manufacturing demand rises. For smaller projects, the company also offers a modular environment, called the KUBio box, which is designed to fit into existing facilities or newly constructed shell buildings. The latest version – the KUBio box for Viral Vectors – is, as you may have guessed, specifically designed for viral vector manufacture, and is based on single-use technology embedded within a biosafety level 2 (BSL-2) environment.

We get the development story behind the Box from Olivier Loeillot, Senior Vice President, Bioprocessing at Cytiva, who is considered the father of the KUBio concept.

How did KUBio begin?

Back in 2010 when I was working for Lonza, I bumped into Kieran Murphy, then CEO of GE Healthcare, at an airport. We got talking and soon realized we had similar ideas – we both wanted to move from providing consumables and hardware to providing complete manufacturing plants. The idea was to combine many products and services into a single offering.

When I subsequently joined GE, Kieran and I had to start from scratch; making our chat a reality by devising a product that customers would be interested in was not going to be easy. We only had a tiny team, but we could see that pharma companies wanted to move from costly, stainless-steel plants towards smaller, more agile, and less costly solutions – without compromising quality. At the same time, the biopharma industry was also beginning to take shape in China and India, and there was huge demand for high-quality facilities that could be built faster and more cost effectively than traditional stainless steel plants. Foreign companies were also looking to create regional capacity in these countries quickly.

There was also rising interest in single use technology, which informed our acquisition of Xcellerex in 2012. We designed the first KUBio in 2012 – which included single-use technology (our FlexFactory biomanufacturing platform) as a key technology.

What challenges did you face in development?

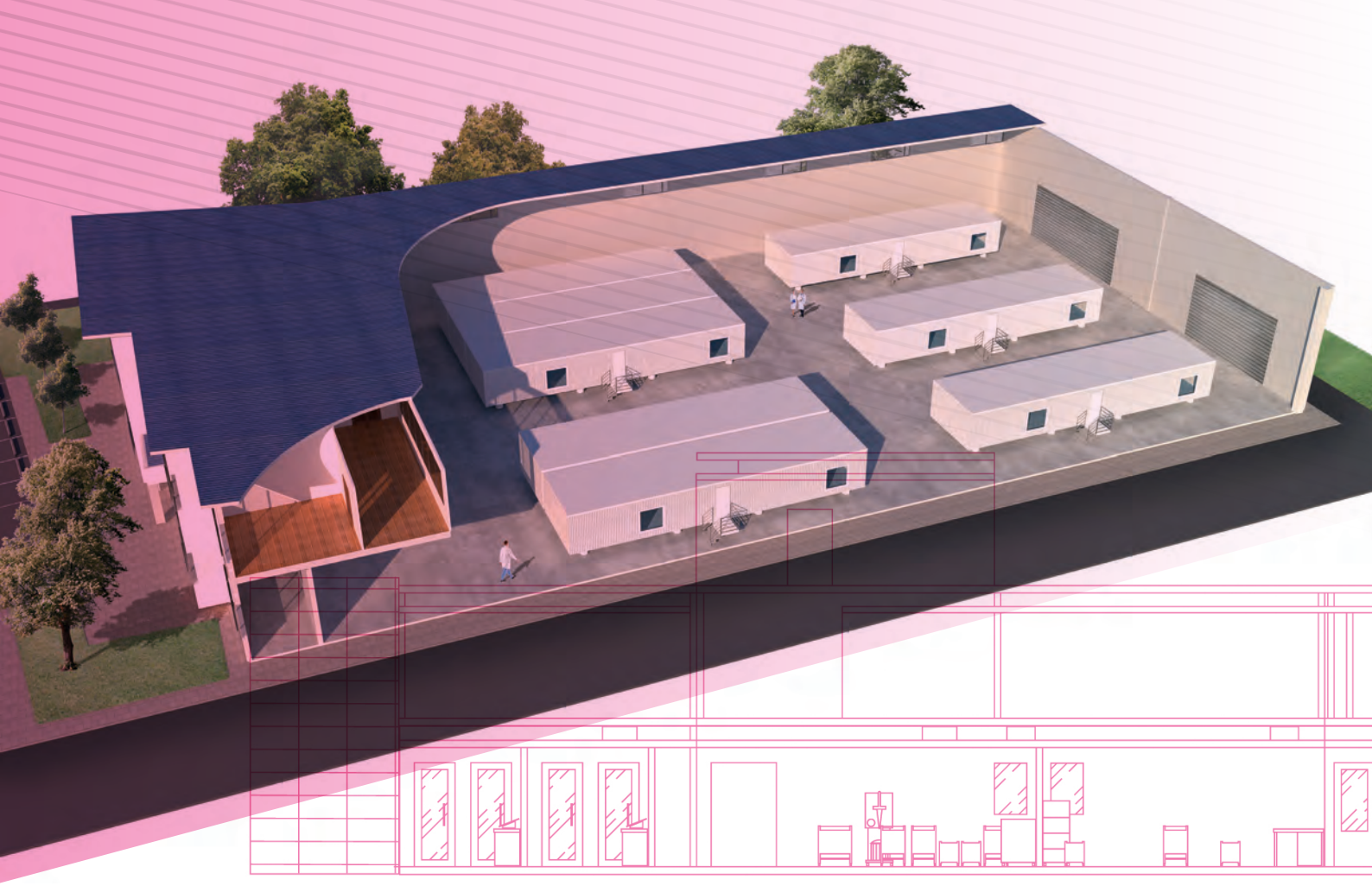
Other companies have previously attempted to introduce modular bioprocessing solutions, but many have failed. When we were designing KUBio, we had a simple goal: figure out the problems and remedy the causes. Our analysis suggested that previous failures were likely due to insufficient appreciation of the importance of localization. Non-localized manufacture of a modular facility, followed by export – and the associated transport expenses, shipping time, import taxes, and so on – will rapidly erode the time and cost advantages of a modular approach. And that's why we opted for local manufacture of KUBio with partner companies.

Another challenge was the perception of modular plants – some saw them as low-cost, low-quality options. Accordingly, we applied state-of-the-art quality standards to modular construction. I think the results are clear; KUBio plants have been running for six years now without problems. Modular plants are evidently not inferior to conventional plants.

What types of companies adopt KUBio?

At first, we thought the KUBio concept would mainly suit small biotechs in emerging markets – those companies that need support and expertise to establish a manufacturing plant. JHL Biotech Inc. (now Chime Biologics) was one of our early customers. They wanted to get ahead of the market and establish a new facility in China – and we were able to support them. Similarly, we helped another Chinese company, BeiGene, to evolve from manufacturing biosimilars to making innovator biologics; KUBio and FlexFactory were key in this endeavor. Today, BeiGene is a global name with several big pharma collaborations.

We were surprised, however, to see that modular manufacturing was also of interest to big pharma. Recently, for example, we designed a state-of-the-art biosimilars plant for Pfizer in China. We also supported the initiation of Pfizer's Chinese operations. We expect to see products from Pfizer's KUBio plant on the Chinese market very soon. And now we are setting up a Chinese manufacturing plant for Lonza, which should be operational in 6-12 months.



"We could see that pharma companies wanted to move from costly, stainless-steel plants towards smaller, more agile, and less costly solutions – without compromising quality."

How does the KUBio box differ from KUBio facilities?

The Box is designed to fit inside an existing building; its footprint is only 800–1,000 square meters. The original KUBio facility is two or three times larger and can sit outside. Deploying a Box allows companies to easily add new capacity or repurpose existing facilities at a fraction of the cost of an entirely new plant. Because the Boxes are small, they allow for high flexibility. For example, one client has requested a triple KUBio box installation incorporating a cell therapy KUBio, a gene therapy KUBio and a fill-and-finish KUBio box – all next to each other in a single shell. The Boxes are suitable for small volume manufacturing – and there is increasing demand for this in the industry. Because of the smaller footprint, however, the Box does not incorporate manufacturing peripherals or process liquids. The assumption is that clients will already have these capabilities and resources.

How has the KUBio concept kept pace with market trends?

We started with KUBio for monoclonal antibodies, but in recent years we have developed a BSL-2 KUBio, the Cell Therapy KUBio for CAR-T products, and now we're deploying the KUBio box for Viral Vectors. The platform is particularly important at present because of the crippling lack of capacity in the gene therapy manufacturing sector – it is not uncommon for biotechs seeking CDMO-mediated manufacture of their viral vector to have to wait 18 months for a manufacturing slot! Such companies urgently require an option that gives them

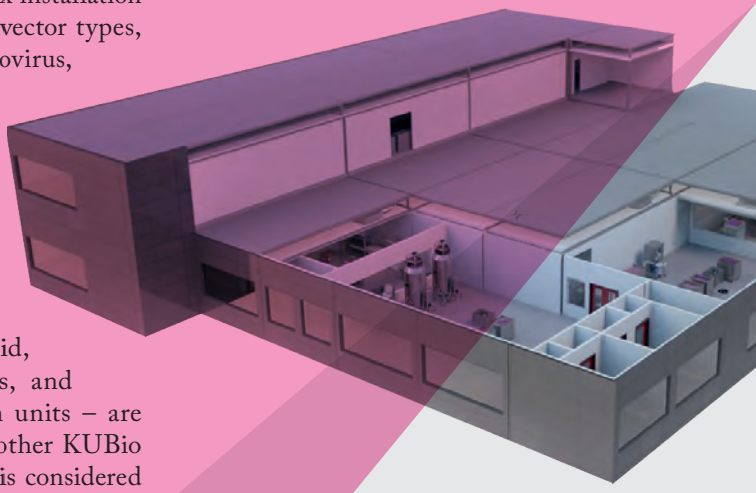
Challenges and Opportunities in Viral Vector Manufacture

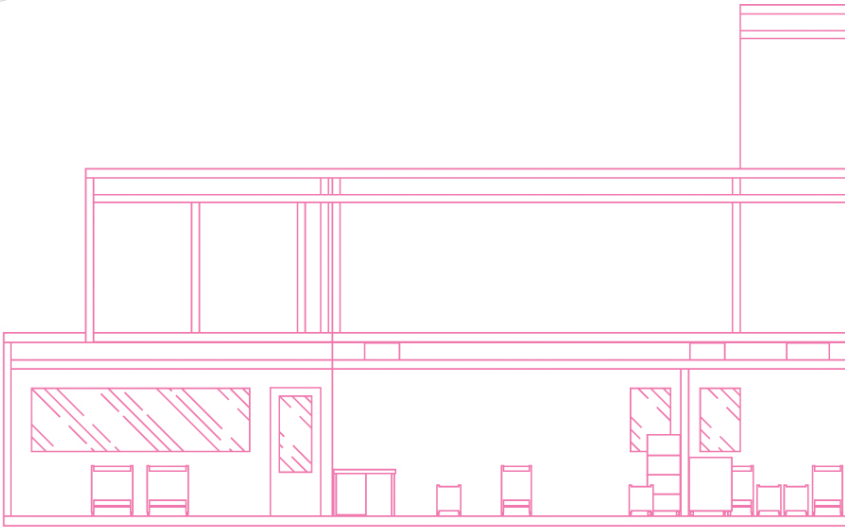
Joe Makowiecki has worked in the bioprocessing field for 25 years, and now oversees the deployment of Cytiva's KUBio facilities, KUBio box systems, and FlexFactory single-use biomanufacturing platforms

I'm very excited to be working in the advanced medicine field. These therapies could have a tremendous impact on human health, but the field is not yet mature and needs a little extra help. Viral vectors today are in a similar position to monoclonal antibodies a decade or two ago, but viral vectors have many unique challenges. Viral vectors are relatively unstable and their complex structures are susceptible to degradation by shear, pH, and temperature. Furthermore, operator safety demands relatively high safety standards – BSL-2 rather than BSL-1 – which places constraints on the design and construction of the manufacturing plant. Essential safety features include adequate segregation, single-pass air systems, and carefully designed workflows. Elsewhere, there is still room for improvement in various areas, including virus production and viral titer optimization, as well as in downstream processes, such as vector recovery. Processes and technologies will continue to improve and evolve as the industry gains experience with viral vector manufacture – and I hope that our KUBio product platform will reflect the industry's evolution by helping it to accommodate the exciting new therapies and processes we now see in development.

The gene therapy market is growing at about 34 percent per annum (compound) and there has been a huge increase in clinical trials. Many gene therapies rely on viral vectors, which explains the industry's severe capacity deficit, that Olivier alluded to. In many cases, CDMOs just cannot keep up with demand – and given how exciting these therapies are, it's heartbreaking that companies have to wait so long to find capacity. We thought our KUBio concept would help plug the gap, which is why we adapted the technology to create the KUBio box for viral vector manufacture. The original KUBio concept was designed with simplification, standardization, speed to manufacture, and flexibility in mind. However, we realized it could be even more versatile, so we modified it to fit into shell buildings. The KUBio box takes our FlexFactory single-use biomanufacturing platform and surrounds it with a cleanroom environment. There are actually a lot of existing spaces in pharma facilities; the space may not be big enough to put in new stainless steel infrastructure, but it can be used to "drop in" a KUBio box – at most, the box requires a very simple shell building. The FlexFactory itself is also very configurable and allows a single KUBio box installation to manufacture multiple vector types, including lentivirus, adenovirus, and adeno-associated virus, and to rapidly scale production on demand. The beauty of the Box is that it is part of a standard platform as the components – upstream bioreactors and mixers, process liquid, chromatography systems, and tangential flow-filtration units – are similar to those used in other KUBio models. Standardization is considered crucial by many of our clients because they want to roll out local production for viral vector based therapies to help bring costs down. Centralized production is considered too expensive because of the transportation involved. Replicating a process for a complex CAR-T therapy is much easier if you have exactly the same equipment and set up at different sites. At the same time, clients can tweak the system in various ways to suit their exact process needs – we offer all kinds of a la carte buffer preparation and fill/finish options. Many clients appreciate this support; instead of struggling with many separate decisions regarding choice of GMP equipment, automation layer, consumable, and so on, they simply adopt an end-to-end, standardized single-use platform. We also take care of project management, delivery installation, commissioning, and qualification. KUBio is truly turnkey.

In my view, nothing beats modular systems in terms of speed and predictability. They are built inside so progress is fast and there is far greater control. With conventional stick-built facilities, on the other hand, there can be labor- and weather-related delays, and issues with consistency of materials.





"Modular bioprocessing systems are simple, fast to implement, and very cost competitive – crucially, without compromising on high quality standards."

manufacturing autonomy. More specifically, the increasing interest in cell and gene therapy approaches and personalized medicine is driving the increased diversity of biologics and smaller patient numbers per drug. This, in turn, demands approaches that permit manufacture at lower cost and smaller volumes, while retaining the flexibility to rapidly add capacity as required. Modular bioprocessing systems are simple, fast to implement, and very cost-competitive – crucially, without compromising on high quality standards.

What is your view on the future of biologics manufacture?

I think that bioprocess efficiency can be improved by advanced automation – and this is something we'll be focusing on at Cytiva. We've signed an agreement with Rockwell for access to their PlantPAx distributed control technology, which we intend to incorporate into our product range by 2021. We are also working on digital systems that will enable intelligent manufacturing plants that can analyze historical batch data and use artificial intelligence tools to predict outcomes for the in-process batch. These capabilities will also identify key process parameters driving yield or productivity. Ultimately, our goal is for a fully intelligent, digital KUBio. Operators in any part of the world will be able to control multiple KUBio-mediated bioprocesses anywhere else in the world.

More generally – partly due to the COVID-19 pandemic – I believe we will increasingly see countries seeking pharmaceutical autonomy; governments will prioritize localized bioprocessing capabilities so that they have the ability to manufacture treatments for their own populations. Similarly, manufacturers will want the ability to rapidly start the manufacture of a new drug or vaccine and quickly scale up. Modular solutions can meet these goals – and a number of governments have already contacted us to discuss how their countries can become more independent and agile when it comes to drug and vaccine manufacture.

The Innovation Awards 2020

Do you want to share the story behind your technology in a future issue of The Medicine Maker?

In our December 2020 issue, The Medicine Maker will showcase the top technologies to have been released throughout 2020. The final winner will be decided by a public vote and – just like Cytiva – will be able to tell the story behind their innovation in a future issue of The Medicine Maker.

The nomination form for the 2020 Innovation Awards is now live: https://tmm.txp.to/innovation2020

The rules?
The technology must have been released (or planned for release) in 2020 and it must be expected to have a significant impact on drug development or manufacture.

The innovation can be a piece of equipment, IT software, formulation technology, drug delivery method, or any other innovation that you think could fit the bill.

Deadline? The deadline for entry is Tuesday 3 November.

Questions? Contact the editor: stephanie.sutton@texerepublishing.com.

Due to the volume of entries we received, we will only contact those chosen to be highlighted in the December issue.

Glass Matters

The Medicine Maker 2019 Innovation Awards included Schott's Everic glass vials as a deserved runner up. Biopharmaceuticals are filling company pipelines and many of these drug products are highly sensitive, which means that special consideration must be paid to the primary packaging. Not all glass is created equal and using the right glass and can make a huge difference in terms of reducing unwanted effects between the drug and the packaging, and reducing line downtime through reduced breakage.

Why does glass matter in the pharma industry?

Borosilicate glass is considered the gold standard in the pharmaceutical packaging industry. It is chemically resistant and, like glass in general, remarkably strong. It was first developed by Otto Schott in 1911, who also founded our company.

Traditional fill and finish operations for drugs rely on bulk filling processes, which allow for high throughput in a short period of time. However, glass-to-glass contact and the mechanical stress on the containers can create small glass particles that can contaminate the medication. In addition, containers may be damaged or even broken. When highly valuable drugs, such as biopharmaceuticals, are involved, breakage is particularly problematic but, whatever the drug, it results in downtime, maintenance, and overall manufacturing costs. The glass you use matters. Some types of glass are more prone to breakage than others, and some glass is also more prone to interacting with drugs. For example, glass with high alkalinity levels, high pH-shifts, and high conductivity can increase the risk of drug instability.

How does Everic compare with other pharmaceutical glass?

Our main inspiration always comes from the market. Today's drugs can be highly sensitive, so high-quality glass is essential. Everic vials are manufactured using a delamination-controlled forming process, which ensures drug stability while keeping delamination under control. We use an optimized borosilicate glass with improved hydrolytic resistance of the inner surface, namely FIOLAX CHR (Controlled Hydrolytic Resistance). The containers are extremely chemically stable and have a homogeneous surface, and all aspects of the glass manufacturing process are highly automated and supported by operational data control. We also use mathematical modeling to optimize the geometry of the vial.

Everic is described as a "modular approach" – what does that mean?

Different drugs and different fill and finish manufacturing strategies have different needs and challenges. With Everic, the customer can choose from one to multiple features to overcome their specific challenges; for example, Everic Pure vials have a chemically homogeneous inner surface to ensure drug stability; Everic Strong uses optimized geometry for improved shock and pressure resistance during the filling process or transport; and Everic Smooth has an outer coating that reduces cosmetic defects in the production processes.

It allows manufacturers to choose the glass that best meets their needs – some drug manufacturers may want all three.

In the future, we aim to introduce other modules. In fact, we've already developed a fourth module, which will be ready for testing and sampling by the end of 2020. I look forward to the official market launch in early 2021…

Shining Excipient Star

Third place in our 2019 Innovation Awards was Colorcon's StarTab – a starch-based excipient for direct compression. Colorcon's Jayesh Parmar tells us more

Why should pharma manufacturers pay careful attention to their choice of excipients?

Before joining Colorcon, I worked as a formulator in the pharmaceutical industry and I've always had a keen interest in excipient science. In fact, from the very beginning, the role and importance of excipients in pharmaceutical dosage forms has blown me away! Excipients play a major role in pharmaceuticals; whether determining release kinetics or improving the flow properties or compressibility of a formulation. Many drugs are difficult to formulate due to their solubility, dose, or stability issues. Excipients are there to make it happen.

As pharmaceutical companies strive to get their products to market in the shortest time, formulators want to develop cost effective yet robust formulations faster and ensure there are no barriers or delays with regulatory approval. To advance through the development milestones, it is imperative to select the right excipient – as well as a trusted supplier, who can provide technical support and understand the regulatory landscape across the world. When it comes to excipients, it can be surprising how regulations differ. Failing to select the right excipient and partner can easily derail the project plan.

What gaps in the market inspired the development of StarTab?

Development scientists have become increasingly interested in formulation simplification using a direct compression tablet manufacturing process, as it helps reduce development time and total cost in-use. Compared with wet or dry granulation methods, the direct compression process is simple and removes multiple manufacturing steps.

Other excipients can be used for the direct compression process; however, the drawback tends to be that formulators need to add a flow-aid and a superdisintegrant. But adding a superdisintegrant adds cost and often results in stability issues because of the high affinity for moisture. Put simply, using StarTab in a direct compression formulation provides desired powder flow, tablet hardness, and disintegration, without the need for the addition of a flow aid or disintegrant.

How does StarTab compare with other starch-based excipients?

Starch-based excipients have a long history of use in the pharmaceutical industry because of their inertness, capacity to remove free moisture in the formulation, and disintegrant properties. StarTab is a modified starch with unique particle shape and size distribution that improve its performance in direct compression while maintaining all the other benefits of starch as an ingredient. Multiple ingredients in a formulation may complicate development (and ultimately the manufacturing process); the effect of each component and its interaction with the API must be considered. StarTab allows scientists to simplify their formulation with a lower number of ingredients and still achieve the desired properties. StarTab also plays an important role in enhancing the stability of moisture sensitive APIs because of its low water activity.

What were the biggest challenges when developing StarTab?

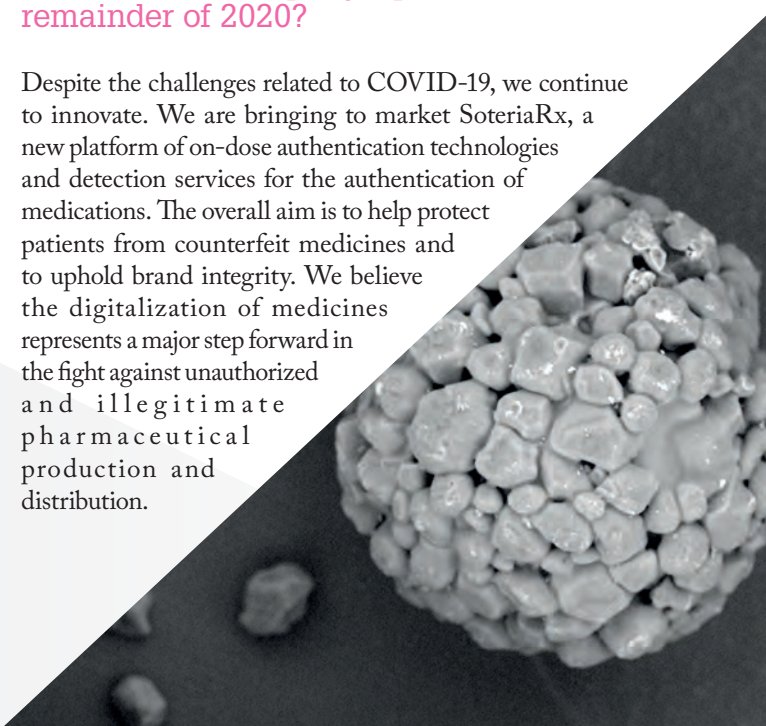
In the eye of the regulator, we had to design an excipient that was novel but not "new" – a significant challenge. And so, throughout development, we had to ensure the product specification met the regulatory requirements without compromising on functionality. From a performance view, the product was developed to produce excellent flow and tablet hardness with fast disintegration – a challenging combination.

How have customers responded?

The market has responded positively! Companies are selecting StarTab for new formulation development projects. And many customers are even changing their existing wet granulation formulation technology to direct compression using StarTab.

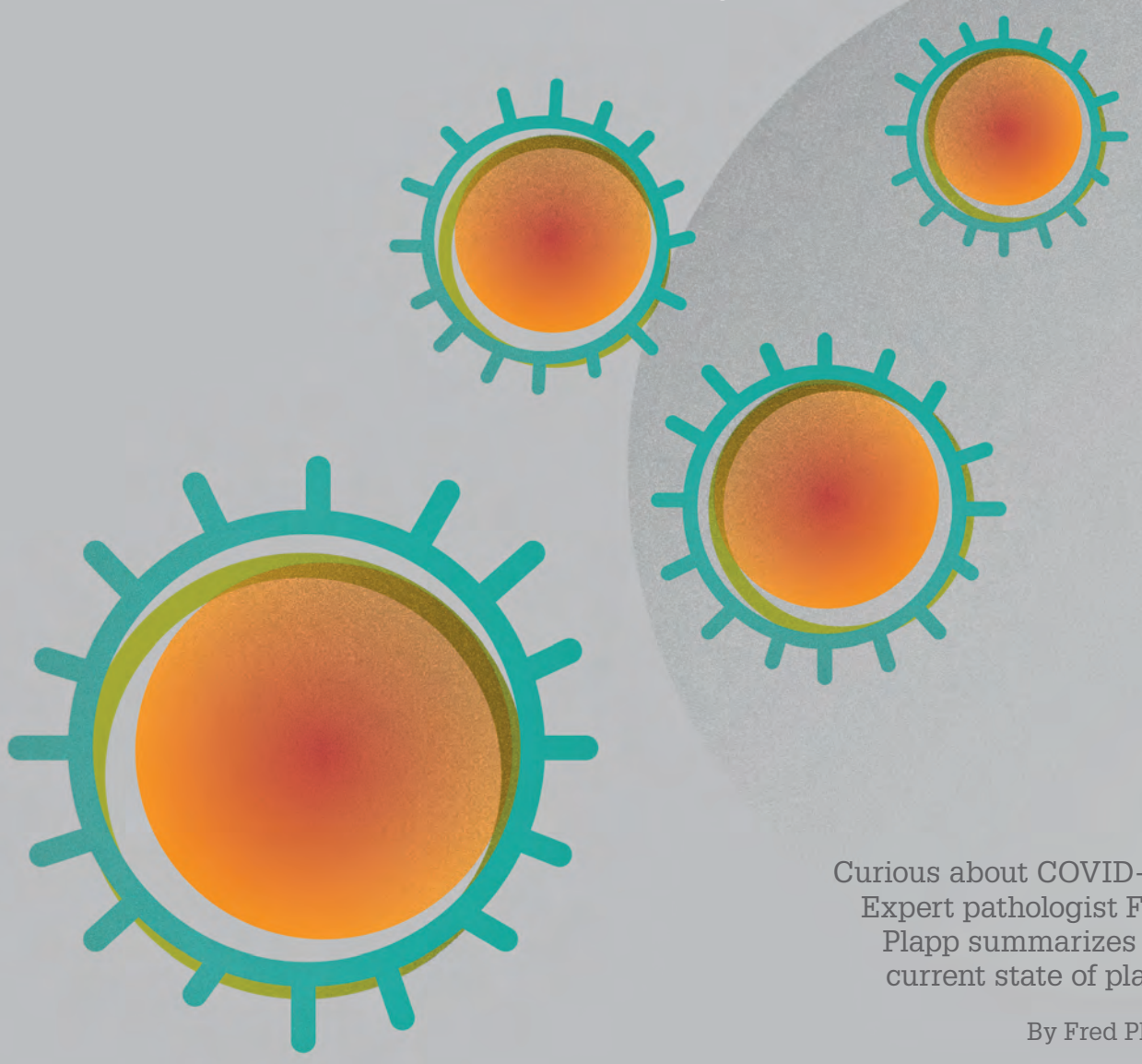
What are the company's plans for the remainder of 2020?

Despite the challenges related to COVID-19, we continue to innovate. We are bringing to market SoteriaRx, a new platform of on-dose authentication technologies and detection services for the authentication of medications. The overall aim is to help protect patients from counterfeit medicines and to uphold brand integrity. We believe the digitalization of medicines represents a major step forward in the fight against unauthorized and illegitimate pharmaceutical production and distribution.



THE COVID-19 PANDEMIC:

A Summary



Curious about COVID-19? Expert pathologist Fred Plapp summarizes the current state of play…

By Fred Plapp

WHAT IS A CORONAVIRUS?

Coronaviruses are a large family of enveloped, non-segmented, single-stranded, positive-sense RNA viruses that circulate among animals including camels, cats, and bats. Coronaviruses derive their name from their electron microscopic image, which resembles a crown – or corona (see Figure 1).

Six strains of coronavirus have infected humans, four of which are together responsible for about one-third of common colds. In the past two decades, there have been three global coronavirus outbreaks (1). The first was Severe Acute Respiratory Syndrome (SARS), caused by a coronavirus termed SARS-CoV. The outbreak started in 2003 in Guangdong, China, and spread to many countries in southeast Asia, North America, Europe, and South Africa. Early cases of SARS were linked to human and animal contact at live game markets. Transmission occurred person-to-person through droplets produced by coughing or sneezing, via personal contact, and by touching contaminated surfaces. In SARS, peak viral shedding occurs approximately 10 days after the onset of illness, when many patients are hospitalized, which explains why healthcare professionals have a particularly high risk of becoming infected. SARS-CoV has a R_0 of 4, meaning that each infected person spreads the disease to an average of four others, and a case fatality rate of 9.5 percent. The virus infected 8,069 persons and caused 774 deaths, and the last known case was detected in September 2003.

Nine years later, MERS-CoV – which causes Middle Eastern Respiratory Syndrome (MERS) – emerged in Saudi Arabia. MERS is characterized by sporadic zoonotic transmission from camels and limited episodes of person-to-person transmission. Explosive nosocomial transmission has been linked to single super-spreaders of infection. Almost all cases have been linked to people in or near the Arabian Peninsula.

The symptoms of MERS are nonspecific, but many patients develop atypical pneumonia and severe acute respiratory distress. Up to 80 percent of patients with MERS require mechanical ventilation. Additionally, patients often have prominent gastrointestinal symptoms and acute kidney failure. This constellation of symptoms is due to the binding of the MERS-CoV S glycoprotein to dipeptidyl peptidase 4, which is present in the lower respiratory tract, gastrointestinal tract, and kidney.

Like SARS, health professionals are at high risk of contracting MERS. The disease is still circulating and, to date, has infected approximately 2,500 people and caused 850 deaths. The main factor that controls the spread of MERS-CoV is its very low R_0 of 1. However, the case fatality rate is very high at 35 percent.

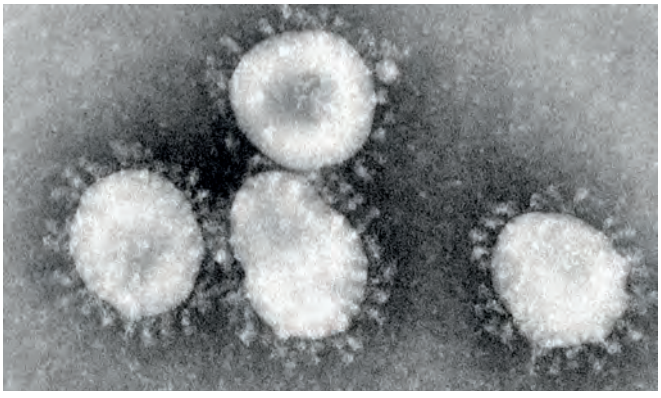


Figure 1. A coronavirus viewed under an electron microscope. *Credit: CDC/Fred Murphy.*

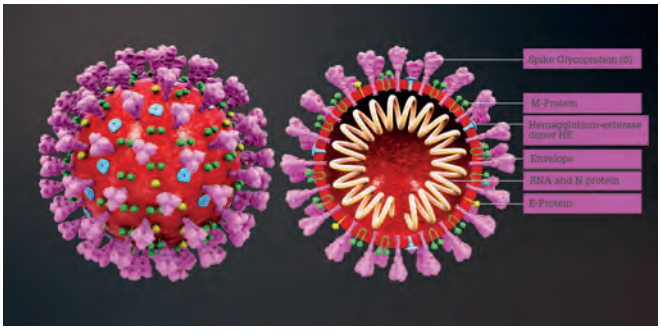


Figure 2. The structure of SARS-CoV-2. *Credit: Scientific Animations.*

WHAT IS SARS-COV-2?

On December 30, 2019, a cluster of patients with pneumonia of unknown etiology was observed in Wuhan, China, and reported to the WHO's China bureau in Beijing. By January 2, 2020, the full genome of a new coronavirus (SARS-CoV-2) had been sequenced by Shi Zhengli, a coronavirus expert at the Wuhan Institute of Virology; just over a week later, the sequence had been published and the Chinese National Health Commission warned of its potential danger. The virus was initially referred to as "novel coronavirus 2019" (2019-nCoV) by the WHO – but, on February 11, 2020, it was given the official name of SARS-CoV-2 by the International Committee on Taxonomy of Viruses (2).

SARS-CoV-2 is a betacoronavirus (an enveloped, single-stranded RNA virus) that shares 79 percent of its genetic sequence with SARS-CoV and has 96 percent homology with the RATG13 coronavirus strain in bats. However, unlike bat coronaviruses, SARS-CoV-2 has a spike protein optimized for high-affinity binding to human ACE2 receptors and a functional polybasic cleavage site at the junction of the spike protein's S1 and S2 subunits (a feature that enhances spike protein cleavage and increases viral infectivity).

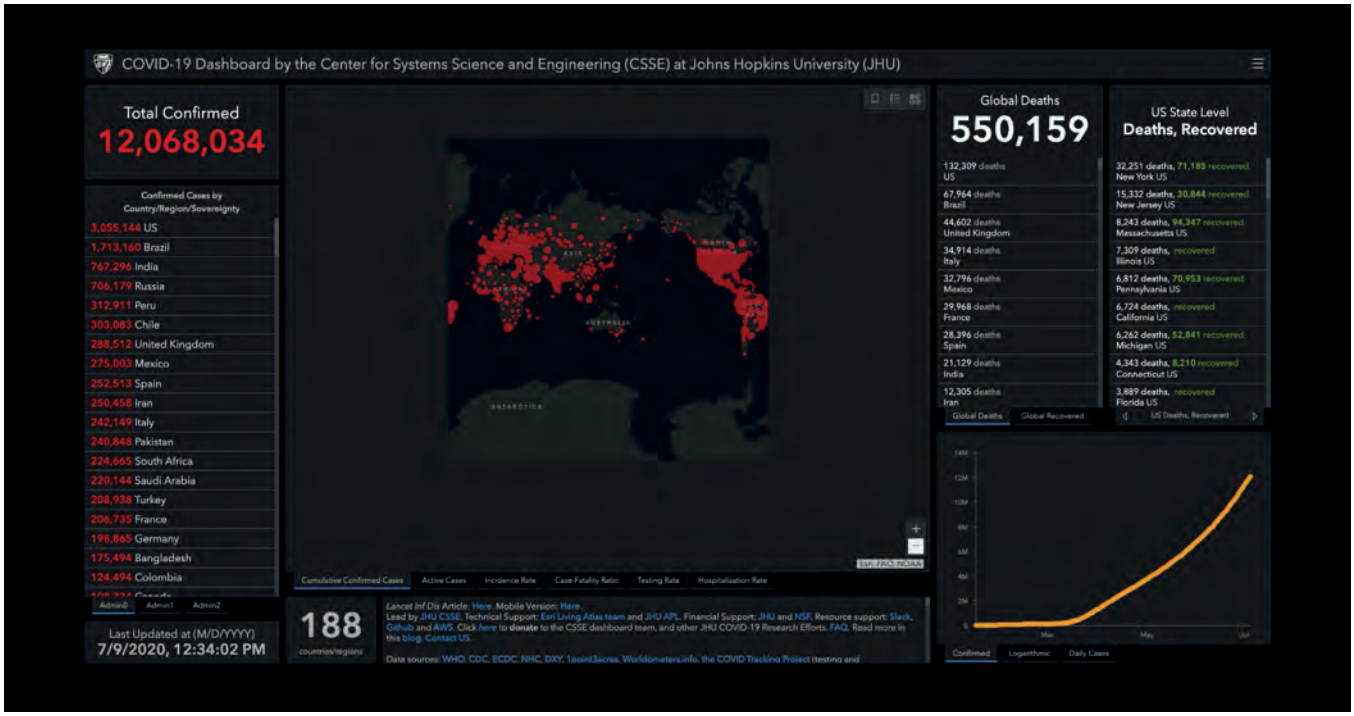


Figure 3. Global COVID-19 cases as recorded by the Johns Hopkins Center for Systems Science and Engineering.

The virion contains four structural proteins (spike, envelope, membrane, and nucleocapsid) and single-stranded RNA (see Figure 2). The RNA genome consists of 29,903 nucleotides – larger than most other RNA viruses. One-third of the genome consists of genes for the four structural proteins and eight genes for accessory proteins that inhibit host defenses. Most of the remainder of the genome consists of the replicase gene, which encodes two large polyproteins that are cleaved into 16 nonstructural proteins (NSP) that assist in replicating and proofreading the viral genome.

SARS-CoV-2 virions attach to human cells with their densely glycosylated spike protein and bind with high affinity to the angiotensin-converting enzyme 2 (ACE2) receptor on human cells. The spike protein is functionally divided into the S1 domain, responsible for receptor binding, and the S2 domain, responsible for cell membrane fusion. Specifically, the RBD of the spike protein mediates recognition of the ACE2 receptor. These receptors are present on many types of cells throughout the body – including lungs, heart, liver, intestines, kidneys, testes, and blood vessels. These cells also possess the TMPRSS2 serine protease, which is needed to cleave the spike protein and facilitate cell entry by SARS-CoV-2.

Once the virus has attached to the ACE2 receptors, the TMPRSS2 protease cleaves the spike protein to expose a fusion peptide. Virions are then able to enter and release their RNA into infected cells, where it is replicated and translated into new viral proteins. Nucleocapsid proteins bind to RNA molecules and are then encapsulated by the envelope, spike, and membrane proteins to form new virions. Infected cells can produce 100 to 1,000 virions per day.

WHERE DID SARS-COV-2 COME FROM?

How the virus evolved to become transmissible to humans is not known, but two theories predominate: either natural selection in an animal host before zoonotic transfer to humans, or natural selection in a human host after zoonotic transfer.

The first scenario is possible because different coronaviruses infecting the same host can exchange gene segments. A bat virus like RATG13 coinfecting an animal with another coronavirus could have acquired a receptor-binding domain (RBD) more adept at infecting humans, leading to SARS-CoV-2. In this scenario, the pandemic would have emerged rapidly as soon as humans were infected because the virus had already evolved to become highly infectious.

In the second scenario, a non-pathogenic version of the virus jumped from an animal host into humans and then evolved to its current pathogenic state. For instance, some pangolin coronaviruses have an RBD structure nearly identical to that of SARS-CoV-2.

A pangolin coronavirus could have been transmitted to a human; these animals are highly valued in traditional Chinese medicine and sold in markets such as the Wuhan Seafood and Wildlife Market, where many early human cases occurred.

Another more provocative theory suggests that SARS-CoV-2 was created (accidentally or intentionally) at the Wuhan Institute of Virology, a facility with a long history of bat coronavirus research. These theories suggest that the virus was either intentionally or accidentally released into the surrounding community. Although the lab has researched recombining the genomes of coronaviruses from different species to determine their potential to infect human cells, prominent virologists in the US consider it highly unlikely that SARS-CoV-2 could have acquired both of its unique features (a highly infectious RBD and a polybasic cleavage site) in tissue culture.

This type of research is performed in Biosafety Level 4 (BSL-4) laboratories, which provide the highest level of biocontainment and follow the most stringent biosafety protocols. However, pathogen leakage from BSL-4 labs has been documented on several occasions. The world's last known case of smallpox was caused by a leak from a British laboratory in 1978; an outbreak of foot and mouth disease in 2007 had a similar origin; laboratories in the US have accidentally released both Ebola and a deadly strain of avian influenza; and Chinese laboratory workers have been infected with SARS-CoV and transmitted it to outside contacts on at least two occasions. Today, there are approximately 70 BSL-4 laboratories in 30 countries, with more planned. Many scientists fear that, with so many biologists actively hunting for bat viruses and performing gain-of-function experiments, the world is at increasing risk of a laboratory-derived pandemic.

WHAT IS COVID-19?

The disease caused by the SARS-CoV-2 virus. According to the Johns Hopkins Center for Systems Science and Engineering, as of June 26, 2020, there have been over 10.1 million confirmed cases of COVID-19 and 502,589 deaths worldwide (3) – but these numbers are still growing steadily (see Figure 3). Globally, the confirmed case fatality rate is above 5 percent – that is, one in every 20 people with a confirmed positive COVID-19 test has died of the disease.

The first US COVID-19 patient was diagnosed in late January. As of June 26, 2020, there have been 2,422,312 confirmed cases of COVID-19 in the country and 124,415 deaths. The average number of new cases per day in the US peaked at 31,000 on April 10, 2020, and then slowly declined to a plateau of approximately 22,000 per day. A few weeks after reopening the economy, however, the number of new cases per day has increased steadily up to 33,000. Current models estimate that between 3 and 10 percent of Americans (between 10 and 33 million people) have been infected so far.

Fortunately, the number of deaths per day in the US has decreased from over 2,000 per day in April to approximately 600 per day in mid-June. The decrease in deaths may be explained by a shift to infections of younger people, continued protection of older people, more testing of people who are asymptomatic or have mild symptoms, and better treatment. Other countries have not experienced this disconnect between the increase in new cases per day and the number of deaths per day – but, because deaths lag behind new cases by approximately three to four weeks, deaths in the US are expected to rise again.

The incubation period before the onset of COVID-19 symptoms ranges from one to 14 days, with a median of 5–7 days. Patients, who have a median age of 59 years, present with fever, dry cough, loss of smell or taste, shortness of breath chills, rigor, fatigue, myalgia, headache, sore throat, and diarrhea.

COVID-19 has a broad clinical spectrum, ranging from asymptomatic infection or mild upper respiratory tract illness to multifocal pneumonia, respiratory failure, and death. Approximately 80 percent of patients experience mild to moderate disease, 15 percent have a severe course requiring intensive care, and 5 percent require mechanical ventilation. Patients may develop pneumonia towards the end of the first week of infection. The mean interval from onset of symptoms to hospitalization is between 9 and 12 days; mean duration from symptom onset to discharge from the hospital is 25 days.

The most severe cases develop pneumonia and acute respiratory distress syndrome (ARDS). Vital signs predictive of a severe course include respiratory rate over 24 breaths per minute, heart rate over 125 beats per minute, and oxygen saturation over 90 percent on room air.

Risk factors for COVID-19 include:

- older age
- ethnicity
- male gender
- comorbidities (including hypertension, diabetes, coronary artery disease, chronic lung/kidney/liver disease, cancer, hematologic malignancy, organ transplant, or immunosuppression)

People with underlying health conditions are six times more likely to be hospitalized and 12 times more likely to die from the disease compared with patients who had no pre-existing conditions.

Approximately 30 percent of hospitalized COVID-19 patients develop progressive pulmonary disease. The major cause of COVID-19 mortality is respiratory failure secondary to ARDS

and thrombosis. ARDS is characterized by leakage of fibrin-rich fluid from pulmonary capillaries into alveoli. It may be caused by direct binding of SARS-CoV-2 to ACE2 receptors, which regulate the production of angiotensin, on endothelial cells. Impairment of ACE2 activity may lead to activation of the kallikrein-bradykinin pathway, which in turn increases vascular permeability. Infected endothelial cells also express leukocyte adhesion molecules that recruit activated neutrophils and lymphocytes to the site of injury. The accumulation of cytokines, neutrophils, and lymphocytes causes inflammation, loosens endothelial cell junctions, increases vascular permeability, promotes alveolar fluid retention, and enhances pulmonary tissue damage.

A recent autopsy report compared the histologic patterns of lungs from patients who died from influenza with patients who died from COVID-19. Both groups had diffuse alveolar damage with hyaline membranes and perivascular T-lymphocyte infiltrates. The lungs from COVID-19 patients had distinctive vascular features due to SARS-CoV-2 invasion of endothelial cells, including disruption of cell membranes and severe endothelial injury. This caused microangiopathy and widespread thrombosis in the small vessels and capillaries of the lungs. Alveolar capillary microthrombi were nine times more prevalent in patients who died from COVID-19 than in those who died from influenza.

Recent reports from Europe and North America have described clusters of children and adolescents requiring admission to intensive care units with Pediatric Inflammatory Multisystem Syndrome (PIMS) associated with SARS-CoV-2 infection. The syndrome has many overlapping features with Kawasaki disease. Thus far, children have been given anti-inflammatory treatments, including parenteral immunoglobulin and steroids.

WHAT ABOUT ASYMPTOMATIC DISEASE?

Early identification and testing of individuals with COVID-19 symptoms have been the primary focus of public health mitigation. However, many studies have shown that a significant proportion of individuals infected with SARS-CoV-2 do not have any symptoms at the time of testing.

Infection rates vary widely between populations. (However, in all studies, the proportion of individuals who were symptom-free when they tested positive was consistently high. Because these studies tested circumscribed populations, the percent of people who are asymptomatic and test positive is likely overestimated. Some experts suggest that the asymptomatic rate is 40 to 45 percent.

Asymptomatic patients have the same viral load as many symptomatic ones and can transmit the virus for at least 14 days. And the absence of symptoms in people infected with SARS-CoV-2 does not mean that they are free from harm; of the asymptomatic individuals who had lung CT scans, 33–48 percent had ground glass opacities.

HOW IS COVID-19 TRANSMITTED?

Two factors facilitated the initial rapid spread of COVID-19 in Wuhan: i) a population of 11 million inhabitants that increased the chance of person-to-person contact, and ii) the city's busy transportation hub, which increased the likelihood of exporting cases to other locations. Despite Chinese containment measures, COVID-19 has grown into a full-blown pandemic.

The R factor, a virus' basic reproductive number, is referred to as R_0 – the average number of people someone carrying the virus will infect. The higher the R_0, the faster an epidemic can spread. At the start of the pandemic, R_0 for SARS-CoV-2 was estimated at 2.0 to 2.5, indicating that one patient could transmit the virus to two (or slightly more) other people. The doubling time for COVID-19 cases is estimated at three to six days.

The virus is transmitted primarily through droplets 5–10 µm in diameter, released when an infected person coughs, sneezes, talks, or even exhales. These airborne droplets can attach to the respiratory tract mucosa or conjunctiva of another person. They can also settle on surfaces or fomites and be transferred to another person upon contact. SARS-CoV-2 is more stable on plastic and steel (up to three days) than on cardboard (up to one day) or copper. Viral transmission is possible if someone touches their face, eyes, nose, or mouth following contact with contaminated surfaces or fomites.

Transmission may also occur through aerosols, which are particles smaller than 5 µm. SARS-CoV-2 remains viable in these particles for up to three hours. Aerosol transmission is a serious risk to health care workers during procedures such as intubation, bronchoscopy, suctioning, turning a patient to the prone position, or disconnecting a patient from the ventilator.

Some experts estimate that exposure to as few as 1,000 SARS-CoV-2 particles can cause infection. One releases about 3,000 respiratory droplets that travel at 50 miles per hour; most are large and quickly fall to the ground, but many remain airborne and can travel across a room in a few seconds. A sneeze releases about 30,000 droplets traveling up to 200 miles per hour, most of which are small and travel great distances. A single cough or a sneeze emitted by an infected person may spread as many as 200 million virus particles.

In contrast, a single breath releases only 50 to 5,000 droplets, most of which travel at low velocity and drop quickly. Because breath is expelled at low force, viral particles residing in the lower

respiratory areas are not expelled – meaning that breathing may release as few as 20 to 30 viral particles per minute. Speaking increases the release about tenfold (200 virus particles per minute), so five or more minutes of face-to-face conversation could lead to infection.

But infection with SARS-CoV-2 depends not only on dose, but also exposure time. If an infected person coughs or sneezes directly toward someone, they can inhale 1,000 viral particles in a few minutes. If someone enters a room shortly after an infected person coughs or sneezes, it may take only a few breaths – whereas if they simply occupied a room where an infected person was breathing, it might take 50 minutes or longer to inhale an infectious dose.

HOW DEADLY IS COVID-19?

The mean duration from symptom onset to death is 18 days. Case fatality rate (CFR), which is calculated by dividing the number of deaths by the number of known cases, has been reported at 6.4 percent worldwide – significantly higher in older patients. But CFR almost certainly overestimates the true lethality of the virus. The number of confirmed cases usually includes only people whose symptoms were severe enough to be tested, resulting in a severity bias. Epidemiologists estimate there are five to 10 times more people with asymptomatic infections. Additionally, the number of deaths may be inaccurate at the time of calculation because deaths typically occur one to two months after a person becomes infected and not all deaths are apparent at the same time. COVID-19 deaths that occur at home are underreported compared with those that occur in a hospital.

The infection fatality rate is the proportion of infected people who will die from COVID-19, including those who do not get tested or become symptomatic. The infection fatality rate is estimated to be between 0.5 and 1 percent. Even at this rate, COVID-19 is a serious public health threat. For comparison, the infection fatality rate of seasonal influenza is approximately 0.1 percent – and it nevertheless kills hundreds of thousands of people each year.

If one assumes that the number of asymptomatic or minimally symptomatic cases is several times as high as the number of reported cases, the case fatality rate may be less than 1 percent. Even though its case fatality rate is lower than MERS-CoV, SARS-CoV-2 will cause many more deaths, because there have been – and will continue to be – so many more cases. As with other coronaviruses, health care-associated transmission appears to be a major mode of infection.

CDC guidelines state that routine BSL-2 laboratory practices are adequate for specimens from patients that may have SARS-CoV-2 infection, with the exception that potentially infectious specimens from these patients should be manipulated only in a biological safety cabinet. The CDC explicitly recommends against viral culture from specimens that may contain SARS-CoV-2. However, clinical laboratory staff should wear PPE and implement standard, contact, and airborne precautions, including the use of masks and eye protection.

HOW DOES COVID-19 RT-PCR TESTING WORK?

The sequence of SARS-CoV-2 was published by Chinese scientists on January 11, 2020; the following week, virologists in Berlin, Germany, produced the first reverse transcriptase real-time polymerase chain reaction (RT-PCR) diagnostic test for COVID-19. This test was supplied to the WHO and many countries adopted it. Unfortunately, the US Centers for Disease Control and Prevention (CDC) refused to employ this test and prevented laboratories from producing their own assays. On February 5, the CDC began shipping its own SARS-CoV-2 RT-PCR kit – but it produced unreliable results and was deemed unusable. Although the problems were raised on February 7, more than 50 days passed before the CDC developed an alternative test. Even after kits became available, testing was hampered by a shortage of RNA extraction reagents and nasopharyngeal swabs.

Eventually, the CDC published primers, probes, and protocols. The FDA issued new guidance on February 29, so that labs could develop and use COVID-19 molecular diagnostic tests (but had to apply for Emergency Use Authorization, or EUA, within 15 business days of clinical use). Although clinical labs could purchase primers and probes for the CDC assay from Integrated DNA Technologies (IDT), other reagents had to be procured elsewhere. To remain in FDA compliance, labs had to follow the exact specifications under which the EUA was granted. If they ran the IDT kit on an alternative platform, new EUA approval was required – an ordeal too onerous for most hospital clinical laboratories.

The WHO's RT-PCR assay targets the SARS-CoV-2 envelope gene and the RNA-dependent RNA polymerase gene. If both targets are detected, the result is reported as positive; if only one is detected, the result is reported as inconclusive. The CDC's original assay included three different amplification regions of the N gene; NS3 was designed to detect all SARS-like coronaviruses, whereas the N1 and N2 regions were specific for SARS-CoV-2. The NS3 target produced too many false positive results and had to be eliminated.

Other laboratories and diagnostic companies designed RT-PCR assays that targeted various combinations of the open reading frame, envelope, nucleocapsid, and RNA-dependent RNA polymerase genes. The limit of detection of most such assays was 100 viral copies/mL or higher. Several commercial

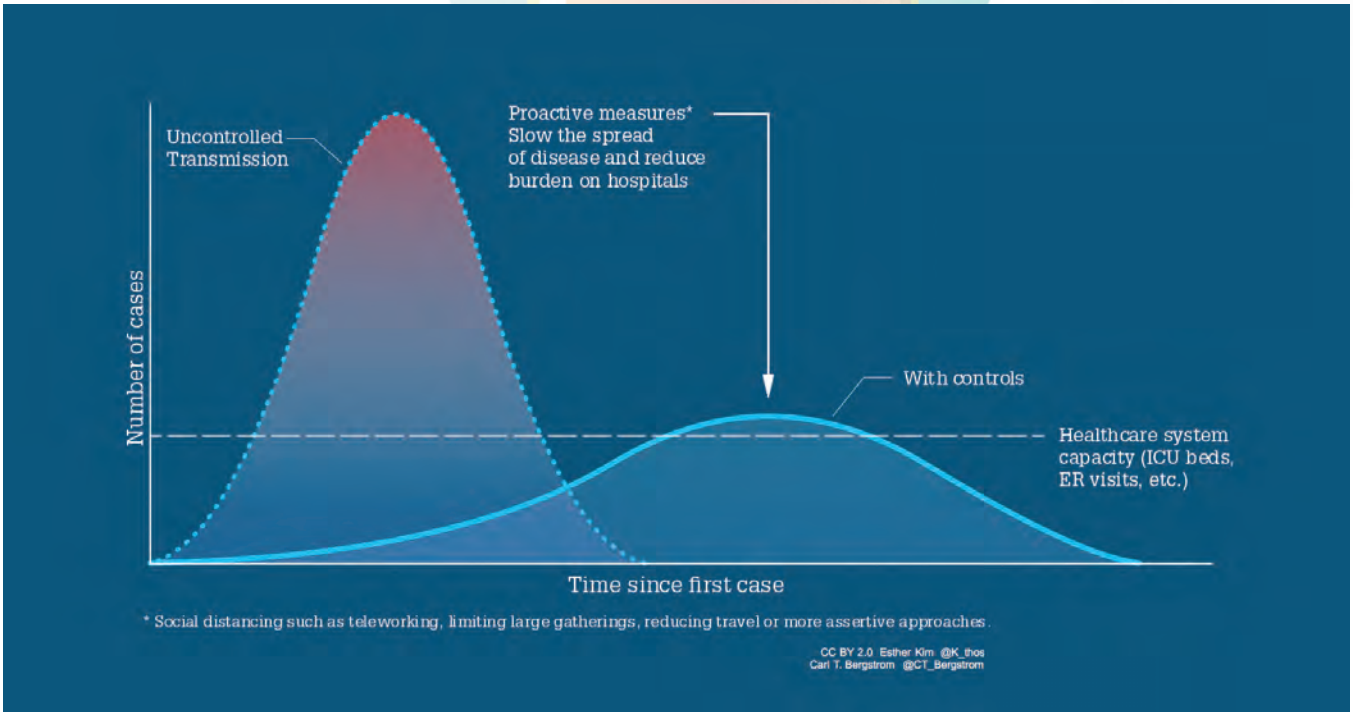


Figure 4. "Flattening the curve," a mitigation approach to lower and delay the epidemic peak. *Credit: Esther Kim and Carl T. Bergstrom.*

reference labs began testing during the second week of March, courtesy of major in vitro diagnostic vendors with EUAs for their assays, but validations for these assays used synthetic RNA sequences spiked into respiratory samples and data documenting their clinical diagnostic performance was limited.

Recent studies indicate that SARS-CoV-2 viral load peaks in the first five to six days of disease onset. Viral RNA can be detected during the second week of disease onset, but viral load is lower. Despite high sensitivity, a negative PCR is insufficient to exclude SARS-CoV-2 infection in patients with a high pretest probability of infection; timing of specimen collection, specimen source, specimen quality, and method performance affect the accuracy of results. If repeat PCR testing is warranted, the second specimen should be performed at 24 hours after the first collection; longer intervals between specimens increases the risk of missed diagnosis because viral load decreases with time.

HOW DOES COVID-19 ANTIBODY TESTING WORK?

Serologic tests detect antibodies that form in blood after SARS-CoV-2 infection. To increase availability, the FDA permits companies to develop and distribute serology tests if they validate the tests with specimens from confirmed COVID-19 patients and notify the FDA of their intent. Results must be accompanied by a statement: "This test has not been reviewed by the FDA."

Over 200 manufacturers have begun marketing serologic tests in the US. Most of the tests flooding the market are lateral flow assays; laboratory-based antibody tests are either enzyme-linked or chemiluminescent immunoassays. Worldwide, concerns have been expressed about the reliability of tests that have been rapidly developed and marketed without rigorous oversight. Some companies claim high sensitivity and specificity without accompanying data, and the FDA has warned that some companies have falsely claimed FDA approval. SARS-CoV-2 antibody tests marketed prior to or without an EUA are not FDA-authorized and have not received a CLIA categorization. These tests are considered high-complexity by default until they receive an approval that permits them to be considered moderate-complexity or CLIA-waived.

Currently available tests target antibodies to one of two SARS-CoV-2 proteins, either the nucleocapsid phosphoprotein or the spike protein. Most lateral flow assays detect IgG and IgM antibodies separately. Enzyme-linked and chemiluminescent immunoassays detect either total antibody, IgG alone, or IgG and IgM separately. There is no substantive advantage to assays that detect IgG over total antibody.

The Infectious Disease Society of America (IDSA) recently published their guidelines on COVID-19 serologic testing (5). They state that antibody testing has not been clinically verified and should not be used as the sole test for diagnostic decisions. Antibody test results should not be used to make staffing decisions or decisions regarding the need for PPE until more evidence about protective immunity is available.

According to the IDSA, SARS-CoV-2 serology may:

- support the diagnosis of COVID-19 in patients who present late and have a negative PCR result, or when lower respiratory tract sampling is not possible
- identify people with an antibody response to serve as convalescent plasma donors
- allow epidemiologic studies of disease prevalence
- verify vaccine response once antibody correlate(s) of protection are identified

Antibody tests should not be used to diagnose acute COVID-19 infections. Individuals with symptomatic COVID-19 generally do not have detectable antibodies to SARS-CoV-2 within 10 days of symptom onset. Most hospitalized patients with confirmed viral RNA have detectable IgG antibodies 14 days after symptom onset; IgM antibodies become detectable only one to two days earlier – so these tests miss infectious patients in the early stages of disease and patients with mild symptoms (who may produce lower antibody titers). They can also fail in elderly or immunocompromised patients, who may not develop detectable levels of antibodies after infection. Even more worrisome, some patients continue to shed viral RNA after seroconversion. A negative serologic test might give patients a false sense of security, leading to reckless behavior.

Antibody tests may play a role in detecting unrecognized past infection and immunity, but that role must be rigorously evaluated. Currently, no one knows how long antibodies to SARS-CoV-2 persist. Seasonal coronavirus antibodies decline only a few weeks after infection and some people are susceptible to reinfection within one year. More encouragingly, SARS-CoV antibodies peak approximately four months after infection and protect patients for two to three years.

The presence of SARS-CoV-2 antibodies does not guarantee immunity. It is not currently known which antibody responses – if any – are protective or sustained. Of COVID-19 patients who developed antibodies during hospitalization, one in three lacked antibodies that neutralized virus in plaque growth assays (the standard test for antibody effectiveness). The best way to investigate immunity is to follow people with and without antibodies to determine whether they become reinfected.

HOW IS COVID-19 TREATED?

The care of patients with COVID-19 is similar to that of patients with other viral pneumonias. It consists primarily of supportive care and oxygen supplementation when needed. Dexamethasone has been reported to decrease the mortality rate of patients with severe respiratory illness (6). Remdesivir, a nucleoside prodrug that inhibits transcription of many RNA viruses, may shorten COVID-19-related hospital stays by an average of three days (7). Tocilizumab, a monoclonal antibody to IL-6, is being trialed in patients with cytokine storm and severe respiratory disease. Additionally, lopinavir/ritonavir (Kaletra), a mixture of two HIV protease inhibitors, is under investigation. Recently, China approved the use of favilavir (Favipiravir), an antiviral drug used for influenza, as an investigational therapy for COVID-19 (8).

Hydroxychloroquine, much touted for its potential therapeutic effect, was shown in 2002 to interfere with SARS-CoV entry into cells – but does not benefit patients with COVID-19. The FDA recently revoked EUA for hydroxychloroquine and chloroquine to treat COVID-19 because neither drug demonstrated benefits that outweighed the risks of dangerous cardiac arrhythmias.

On March 24, the FDA approved the investigational use of convalescent plasma, which contains antibodies to SARS-CoV-2, for patients with serious or life-threatening disease. COVID-19 convalescent plasma (CCP) is a potentially safe and effective, but unproven, therapeutic modality for COVID-19. The FDA requires clinical application of CCP to be conducted under one of three defined pathways: i) an IND application to support research; ii) an emergency use IND for compassionate use in an individual patient with severe or immediately life-threatening COVID-19; or iii) a government-led initiative providing expanded access program IND to participating institutions under a master treatment protocol with modest data-reporting requirements.

Several trials have been proposed to evaluate CCP for:

- post-exposure prophylaxis among adults with close contact exposure to COVID-19 who have not yet manifested symptoms
- treatment of patients with confirmed mild disease
- treatment of moderately ill, hospitalized patients who have not been admitted to the intensive care unit admission or required mechanical ventilation
- rescue therapy for patients requiring mechanical ventilation
- safety and pharmacokinetics in high-risk pediatric patients.

WHEN WILL THERE BE A VACCINE?

On May 1, the US federal government launched "Operation Warp Speed" to deliver a COVID-19 vaccine by January 2021, years ahead of standard vaccine timelines. Because of the urgency of the pandemic, some scientists propose using faster "challenge trials," which deliberately expose vaccinated volunteers to the virus and could determine a vaccine's effectiveness in weeks instead of years.

As many as 123 different SARS-CoV-2 vaccine candidates are under development worldwide, 10 of which are in human trials. Many have not been tested in animals. In July, the National Institutes of Health (NIH) will begin randomized phase 3 trials to determine if any of these 10 vaccines prevent SARS-CoV-2 infection. They plan to enroll 20,000 individuals who will receive a vaccine and 10,000 who will receive a placebo.

Conventional vaccines rely on the production of either live attenuated virus or inactivated virus. Live attenuated vaccines use a weakened form of the virus to produce an immune response without causing serious illness. Because they use live virus, these vaccines need extensive safety testing. Some live viruses can be transmitted to others, which is a concern for people who are immunocompromised. Inactivated virus vaccines use a killed virus, which may be safer, but often produces a weaker immune response. These vaccines require multiple doses and boosters to provide long-term immunity. Some vaccines also require adjuvants to enhance the immune response – and work is already underway on licensed adjuvants for use with COVID-19 vaccines.

A vaccine that targets the SARS-CoV-2 spike protein should theoretically prevent the virus from binding to human cells and reproducing. The advent of genetic engineering may also allow scientists to produce novel vaccines that specifically target this antigen. A gene for a single SARS-CoV-2 protein can be introduced into cell cultures, which synthesize large quantities of relatively pure protein to serve as a vaccine. Alternatively, the gene can be inserted into an innocuous virus, such as adenovirus, which is then injected. The genetically engineered adenovirus infects human cells, replicates, and expresses the spike protein to prompt an immune response.

Some companies are attempting to produce nucleic-acid vaccines, in which a gene for a SARS-CoV-2 antigen is introduced directly as a segment of either DNA or RNA. Such vaccines should carry less risk of contamination because they do not require cultured cells or viruses. However, no RNA or DNA vaccine has ever been licensed for use in humans anywhere in the world. DNA plasmid vaccines transfer the genetic blueprint for RNA into cells, which then synthesize spike antigens; one such vaccine was developed for MERS, but never manufactured. RNA vaccines eliminate the need for DNA plasmids by embedding RNA into lipid globules that can merge with cell membranes. Human cells then synthesize the corresponding antigen. RNA vaccines may produce more potent immunity than DNA plasmids, but they are less stable and must be stored frozen.

STOPPING COVID-19 – SUPPRESSION OR MITIGATION?

Some countries attempted to reduce the infectivity of the pandemic to R_0 by enforcing suppression. An R_0 below 1 indicates that each infected person transmits SARS-CoV-2 to less than one other person. Successful suppression requires early and widespread testing – including of people without symptoms. Those who are positive are isolated so that they cannot infect others.

A failure to implement early testing in other countries has forced them to rely on mitigation, rather than suppression, to slow the spread of disease. Mitigation efforts include handwashing, school and business closings, travel limitations, mask wearing, and social distancing to decrease the likelihood of person-to-person transmission. Mitigation focuses on protecting the most vulnerable from the effects of a disease that is already widespread throughout the community. By reducing the number of active cases at any given time, health care providers can respond without becoming overwhelmed (see Figure 4).

The steep, dotted curve represents the occurrence of cases over time without protective measures. The flatter, solid peak illustrates the beneficial effect of mitigation – also known as "flattening the curve." The Center for Infectious Disease Research and Policy (CIDRAP) has predicted that the COVID-19 pandemic will last for 18 to 24 months, and will not be halted until 60 to 70 percent of the population becomes immune (10). Depending on control measures, cases may come in waves of varying impact and at different intervals as illustrated by the following three scenarios.

Scenario 1: The first wave of COVID-19 (spring 2020) is followed by a series of repetitive smaller waves that occur through the summer and then consistently over a one- to two-year period, gradually diminishing in 2021. These waves may vary geographically and may depend on what mitigation measures are in place and how they are eased. Depending on the height of the wave peaks, this scenario could require periodic reinstitution and subsequent relaxation of mitigation measures over the next one to two years.

Scenario 2: The first wave of COVID-19 is followed by a larger wave in late 2020, and one or more smaller waves in 2021. This pattern will require the reinstitution of mitigation measures in the autumn to decrease the spread of infection and prevent healthcare systems from being overwhelmed.

Scenario 3: The first wave of COVID-19 is followed by a slow burn of ongoing transmission and case occurrence, but without a clear wave pattern. Again, this pattern may vary somewhat geographically and may be influenced by the degree of mitigation measures in place in various areas. This scenario would likely not require the reinstitution of mitigation measures, although cases and deaths will continue to occur.

Whichever scenario the pandemic follows, a significant level of COVID-19 infection is likely to continue worldwide, with hotspots popping up periodically in diverse geographic areas. As the pandemic wanes, it is likely that SARS-CoV-2 will continue to circulate in the human population and will synchronize to a seasonal pattern with diminished severity over time, as with other less pathogenic coronaviruses.

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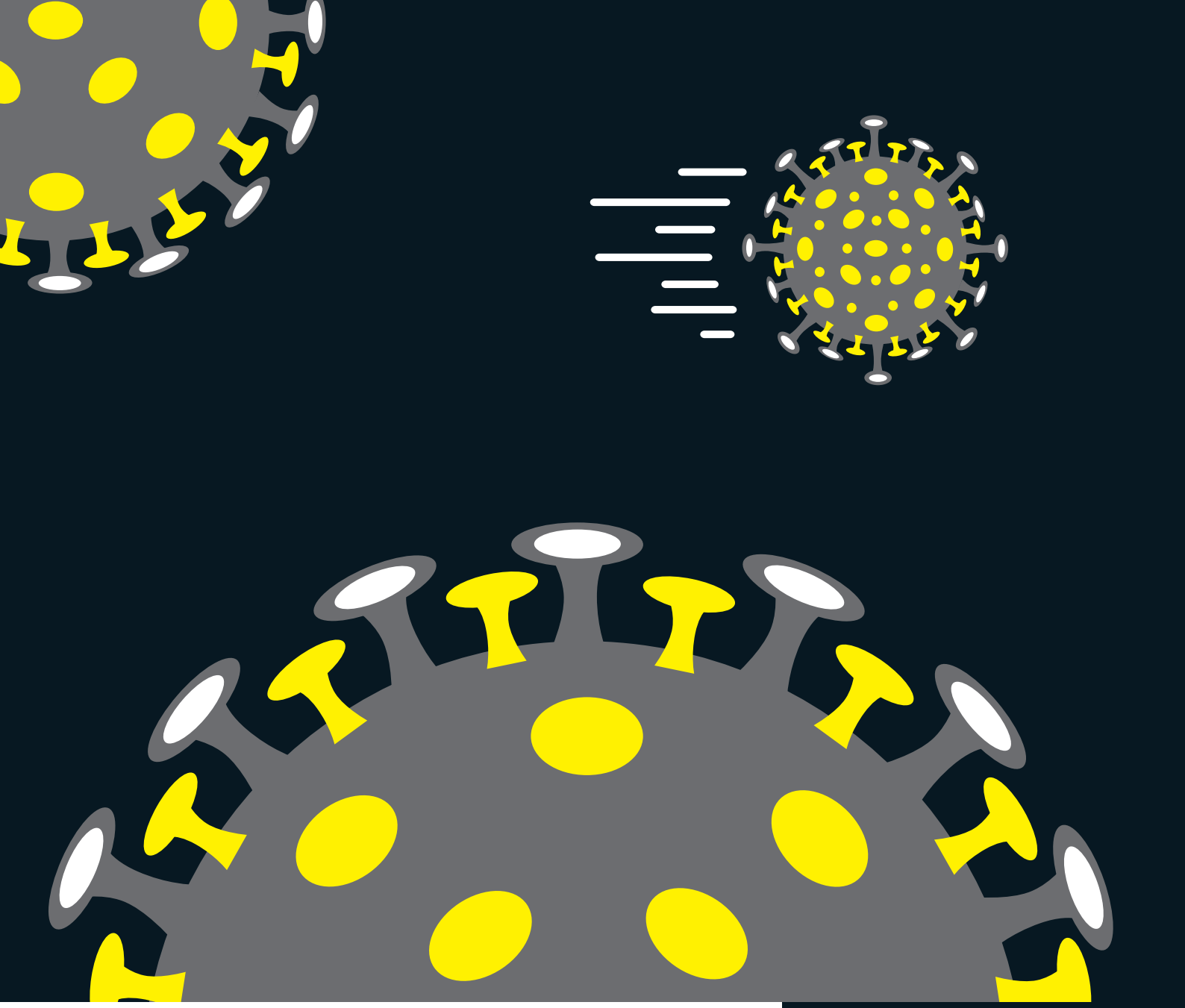

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A Rare Opportunity for Change

With a history of clinical failure in several disease indications, the road to regulatory approval for Koselugo has not been easy. But now it has become the first therapy approved to treat neurofibromatosis type 1 in pediatric patients. Here, we explore its potential impact and find out the lessons learned along the way.

By Maryam Mahdi

Much research and development focuses on the so-called big four cancers (breast, bowel, lung, and prostate), but treatment options for patients living with rarer cancers can be less forthcoming. Neurofibromatosis type 1 (NF1) is one such cancer, affecting one in every 3000–4000 individuals in the USA (1). Triggered by a mutation in the NF1 gene, it causes a variety of symptoms, including patches of brown skin pigmentation (known as cafe au lait spots), tumors underneath the skin, and learning and behavioral challenges. Another significant issue associated with the condition is that up to half of the people who live with it develop plexiform neurofibromas – tumors that can grow along nerve sheaths (1). And because these tumors can grow in various locations and vary in size, they can cause a wide range of symptoms, including reduced mobility, airway and bladder dysfunction, as well as disfigurement. Though treatments exist for these secondary symptoms, no drug was able to address NF1 directly – until now.

Koselugo, a MEK inhibiting drug developed by AstraZeneca, received approval from the FDA in April 2020 to treat NF1 in pediatric patients. During NF Awareness Month (ctf.org), we spoke with George Kirk, Global Medicines Lead, R&D Oncology at AstraZeneca, to uncover the story behind the development of the drug.

How does NF1 affect patients?

Living without medicines that actually treat the condition is a challenge for many patients. From managing breathing with tracheostomies to the need for analgesics (and stronger drugs) for pain management, NF1 patients are fighting against the disease every day of their lives. Though surgery to remove plexiform neurofibromas is available, it is only applicable to around 15 percent of patients, and it is very difficult to remove tumors growing along nerves without causing further damage. In addition, patients who have plexiform neurofibromas also have a greater risk of developing other types of cancer. Up to 15 percent of patients develop malignant peripheral nerve sheath tumors, which can significantly reduce life expectancy.

What is the story behind Koselugo?

Koselugo has been in development for over 16 years. The MEK inhibiting drug was initially developed by Array BioPharma, a subsidiary of Pfizer. The company had just begun early clinical trials in humans when AstraZeneca licensed the product and began its own phase I and II trials. Though MEK inhibitors had previously been shown to be effective in skin cancers like melanoma, they have had limited success in other forms of cancer. The focus of AstraZeneca's trials was to examine the efficacy of the drug in other cancers affecting adults, including uveal melanoma, thyroid, and lung cancers. Unfortunately, the drug failed across three studies between 2013 – 2016.

Although these trials were unsuccessful, the drug hadn't been written off. In 2011, we were approached by the Cancer Therapeutics Evaluation Program (CTEP) and the National Cancer Institute (NCI) in the USA, which was interested in investigating the potential of Koselugo in pediatric patients with NF1 and plexiform neurofibroma. There was a large volume of preclinical data that indicated the possibility of success of the drug for this particular disease indication. Within a few years of conducting the first phase I trials in children, we saw a massive reduction in tumor volume – a positive step forward for a drug that had experienced many setbacks.

In 2014, the NCI presented their phase I trial data at the American Society of Clinical Oncology – a huge moment for our team because it was one of the first major milestones on the road to receiving approval for this drug.

More importantly, it showed us that the science had pointed us in the right direction and that we had been right to stick with Koselugo, despite its failures.

What lessons were learned during the development of the drug?

Finding and collaborating with partners with the right expertise, such as CTEP and the NCI, is important for the development of any product – but more so when a medicine is intended to treat a small patient population. Koselugo was the first drug to be approved for the treatment of NF1 in children, so we were entering new territory when determining the clinical benefit of the drug and putting together a regulatory submission for the FDA. Fortunately, we were closely supported by our colleagues at the NCI, as well as others within regulatory bodies.

It sounds like a rewarding project to be involved in…

I've spent the majority of my career working on oncology projects – and seeing much needed therapeutic options become reality is something I hold dear. Though it's difficult, or arguably impossible, for us who haven't lived with cancer – or specifically NF1 – to fathom what life must be like for these patients, by making a difference in any way possible we can offer our support.

Hearing the individual stories of patients who have partaken in the clinical trials for Koselugo is extremely rewarding. During the course of the trial, we had an example of a six-year-old patient who had tumors and plexiform neurofibromas in her face and neck. Because of the symptoms of NF1, she was unable to breathe without a tracheostomy. While taking Koselugo, the tumors shrunk, enabling her to breathe on her own. Though there is no way of quantifying the impact of the treatment on that particular patient's life, knowing that she was able to regain independence and attain an improved quality of life is motivating to say the least. Overall, the reaction from the patient community has been incredible.

I was lucky enough to speak to the Children's Tumor Foundation – an NF1 patient advocacy group and research organization – about the drug. I had the chance to talk with a number of patients and families, and so it was a very special and humbling call.

Is enough being done to address pediatric cancers?

The short answer is that there is always more that can be done. There's certainly a lot of progress being made in the oncology space, but there are fewer options for the treatment of pediatric cancers than adult cancers. And that reality is highlighted by the fact that the approval of Koselugo was only the third in 20 years for a drug with an initial indication for pediatric cancer.

Advances are being made, particularly in hematological cancers like leukemia, but the pharmaceutical industry needs to devote more resources into treatments for children, and consider pediatric needs much earlier in the development cycle.

Reference

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COVID-19: Llamas to the Rescue

Camelid-derived molecules have been investigated for their potential to treat a wide range of viruses. But do llama antibodies have what it takes to tackle COVID-19?

By Maryam Mahdi

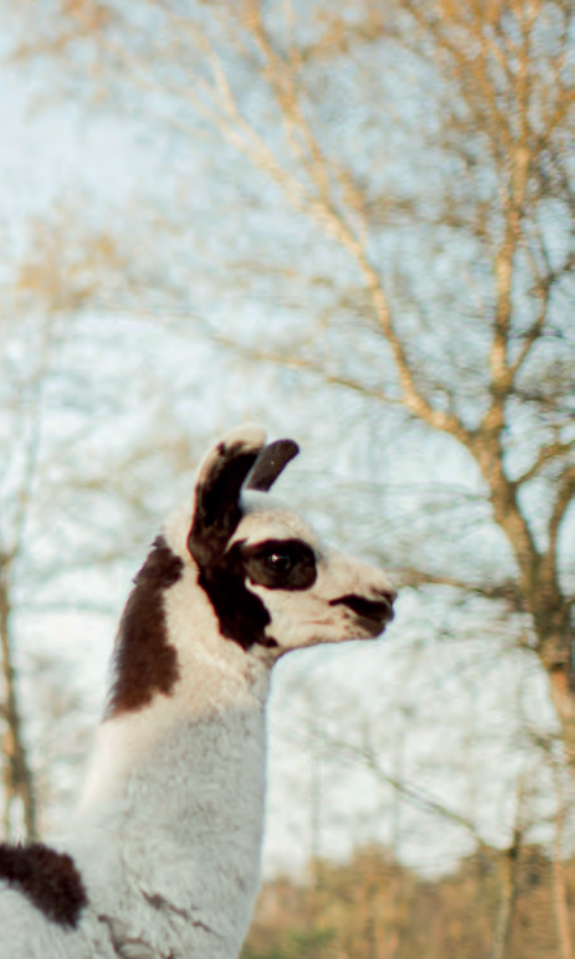
When the COVID-19 pandemic hit, researchers and companies around the world rapidly began to look for solutions to a seemingly unprecedented problem. From the use of drug repurposing platforms to the development of a new vaccine by 2021, many avenues are being explored. A graduate student affiliated with the McLellan lab at the University of Texas at Austin, Daniel Wrapp has found himself right in the middle of the COVID-19 fight. Even before COVID-19 was identified, his postgraduate work had centered on coronaviruses. And so, when the pandemic began, Wrapp and colleagues hit the ground running. In fact, their lab was the first to report on the structure of the protein SARS-CoV-2 uses to invade the host's cells – the now infamous spike protein. "As soon as we were made aware of the genomic sequence of the virus, we set to work trying to resolve its structure," says Wrapp. "We were confident that we'd be able to do it because our lab had determined the structure of several other coronaviruses in the past – and it only took 12 days to complete this time around!"

The research, which was published in Science (1), marked an important step forward in the scientific community's pursuit of a vaccine.

Creating therapeutic options

Wrapp and his colleagues began thinking about vaccines in 2016. They were well aware that the vaccine development process could be long and arduous, and had started to investigate the potential of nanobodies – antibody fragments that can be nebulized and administered to patients through inhalers – as a novel preventative measure against infectious respiratory diseases. These unique

"Using llama-derived molecules may seem unusual, but the protein fragments have a well-established history in antibody research."



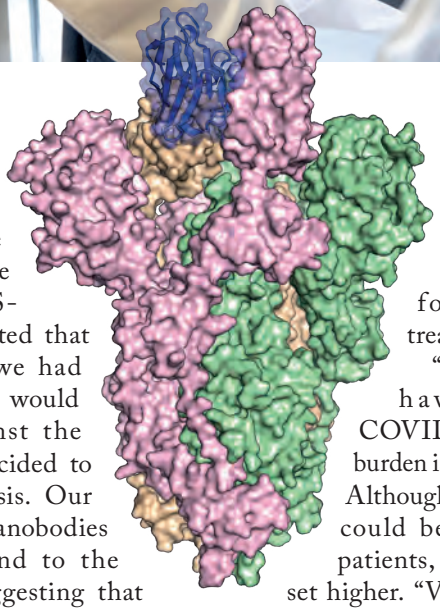
antibodies, derived from llamas, bind tightly to the spike proteins of the viruses causing SARS and MERS, neutralizing them and preventing them from infecting cells in culture (2).

Using llama-derived molecules may seem unusual, but the protein fragments have a well-established history in antibody research. Llamas, like other members of the camelid family, produce two different types of antibodies in response to pathogens – one that bears similarity to human antibodies and another, much smaller nanobody that consists of a single antibody domain. These tiny antibody fragments have previously been investigated for their therapeutic potential across a variety of indications, including Alzheimer's disease, cancer, and infectious diseases.

"We were interested in llama nanobodies because they remain stable when manipulated. We worked with Xavier Saelens, a researcher at Ghent University in Belgium, to vaccinate a llama called Winter with them," says Wrapp. The researchers at Ghent isolated a panel of nanobodies from Winter and shipped them to the McLellan lab for evaluation of their therapeutic potential. "Once we received the nanobodies, we carried out a series of neutralization assays using these molecules and pseudoviruses – synthetic viruses used to inject genetic material into cells. We found two really interesting nanobodies, one of which potently neutralized the MERS coronavirus and another that neutralized SARS."

The pandemic strikes

"As we were writing up the results of our



study, COVID-19 hit the headlines," says Wrapp. "Assessing the structure of the spike protein of SARS-CoV-2, we predicted that the nanobodies we had previously isolated would cross-react against the new virus and decided to test that hypothesis. Our SARS-directed nanobodies successfully bound to the spike protein, suggesting that they might be relevant therapeutic candidates for COVID-19." The team's Ghent-based colleagues then found that introducing two linked nanobodies to SARS-CoV-2 in culture neutralized the virus. The researchers have now started preclinical trials in hamsters to ensure that their treatment is safe and effective. They are also hopeful that their work will be used as the basis for a prophylactic treatment.

"We currently don't have a vaccine for COVID-19 and the disease burden is proving to be severe." Although a treatment like this could benefit symptomatic patients, Wrapp's sights are set higher. "Vaccines aren't always quite as effective in vulnerable groups, such as the elderly, because they can't mount the same active immune response as younger people. In such cases, we could treat people prophylactically with this antibody."

Though it sounds promising, more time and experimentation are needed before this type of treatment enters the clinic. But Wrapp believes it is an encouraging example of how basic research has become useful in an unexpected way. "When we started our research in 2016, both the SARS and MERS outbreaks were behind us," he says. " In all honesty, we just wanted to find out how these spike proteins functioned. Who could have predicted that, four years later, it could help quell another crisis?"

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Driving Antibody Drug Discovery Through GenScript ProBio

Founded in New Jersey in 2002, GenScript is now truly global, with over 2000 employees, several R&D and manufacturing sites across China, and branch offices in Europe and Japan, as well as the USA. The company's new segment, GenScript ProBio, has a strong focus on antibody drug discovery and is joined by business units dedicated to cell and gene therapy and biologics. Here, we speak with Liusong Yin, Executive Director of Biologics Discovery Department at GenScript ProBio, to find out more about operations in China.

How did you join GenScript?

For my undergraduate and PhD studies, I focused on immunology, studying CD4+ T cell and antibody responses against different pathogens. After that, I worked at Pfizer, where I investigated the immunogenicity of therapeutic protein products. My background experience was a good fit with GenScript and I love being in research and working with different molecules – and so I joined in 2015. Today, I'm in charge of Biologics Discovery, which covers antibody drug discovery, in vitro pharmacology, and antibody research. We use various technologies to generate and optimize antibodies, and we also need to develop platforms to validate whether these antibodies are suitable for use. GenScript is both a CRO and CDMO, so constant innovation to ensure we are offering our customers the best technologies is important to us. We certainly push forward via internal R&D efforts, but we also constantly evaluate external innovation – everything from transgenic animals to antibody libraries to new instrumentation.

How has COVID-19 affected your customers?

Many of our customers are developing COVID-19 therapies. We can provide the necessary tools, such as proteins, genes, reagents and assays, to help them discover and develop effective therapies and vaccines. In fact, our business has been growing during the pandemic because of our extensive experience in antibody discovery.

However, we also still have many customers working on regular antibody drug discovery projects. Some of these customers have had to temporarily close their labs, but we can help because they can rely on us for additional capacity and capabilities. Although social distancing and lockdown measures are still in place in many countries, we are fully operational in China. All of our employees have been on site since February, which means we've been able to minimize the impact that the COVID-19 pandemic is having on our customers.

What other trends are influencing drug discovery?

There is a clear trend towards fully human antibodies as some believe they carry less risk for immunogenicity compared with humanized or chimeric antibodies. We ensure we offer each of these options. There are around 80 antibodies approved by the FDA and EMA, including about 30 fully human antibodies and 30 humanized antibodies.

Another trend is the growing popularity of single-domain antibodies (sdAbs); they are easy to work with, have a high expression level, and are very stable and soluble. They can also be used to generate bispecific and multi-specific antibodies. We do have a symmetric bispecific single-domain antibody fused to monoclonal antibody (SMAB) platform that is natural and less immunogenic. In some diseases, we are learning that targeting a single epitope is not good enough. Therefore, drug developers are increasingly focusing on combination approaches and multi-specific therapeutics.

One thing's for sure, keeping up with current trends is crucial for us to understand and anticipate customers' needs.

How do you work with customers?

Simple: we discuss the customer's needs and then recommend the best platform for them, which works well because we have ensured that we have a multitude of cutting-edge technologies that can suit different requirements. We offer our well-established Hybridoma Generation for Therapeutic Antibody Discovery Service, as well as naïve and synthetic libraries. We have libraries for both human and animal antibodies, including single-domain antibodies for llama or alpaca. For clients with urgent projects, we also offer ProSpeed single B cell technology (SBCT), which can shorten the turnaround time by three to six months compared with the hybridoma or library approach. Some clients also like to use a combination of different approaches.

What lies ahead in the future of drug discovery?

The modality of future medicine will be more diverse. There will be not only monoclonal and multispecific antibody drugs, but also antibody-drug conjugates, cell therapies, gene therapies, and more – the industry must explore all approaches to tackle the biggest health issues, such as cancer. GenScript ProBio accelerates drug discovery and development through the cutting edge innovative platforms. We also have new molecular entities (NMEs) drug pipeline to expedite the discovery research to our customers. Our goal is to help our customers bring new therapeutics to market by being part of their antibody discovery processes. We constantly innovate to identify the best platforms and approaches – and we want to see these used to bring benefits to patients everywhere.

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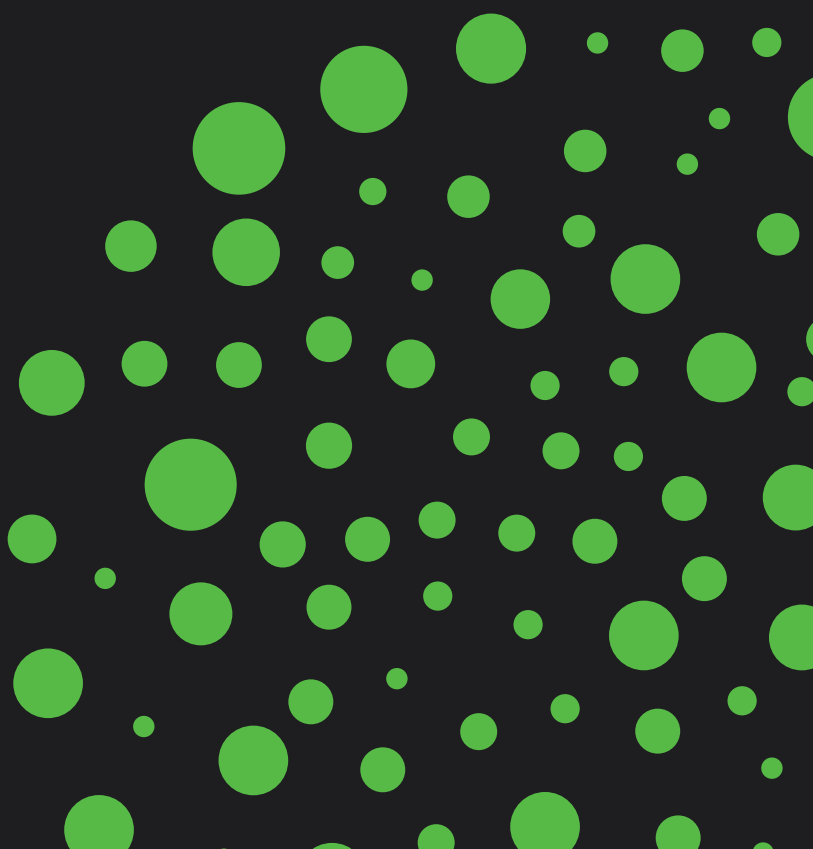

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Business

Economic drivers
Emerging trends
Business strategies

When the Worst Happens

Business insurance exists to help companies when unexpected events and damages occur – so you need to have the right policy in place

If you are a scientist starting up your own business, you'll no doubt be excited and passionate about the science you hope to one day bring to market. But running a company is not just about making the science happen. Businesses require strategies and a significant amount of administrative effort. Insurance is one element of running a business that is easy to get wrong. The business of life sciences comes with unique risks and you need to ensure you are covered if something happens to your laboratory or manufacturing facility. For smaller companies, navigating the insurance landscape can be a minefield. Even though you may not have a commercial product, your R&D will still carry a high value.

We spoke with David McInally from UK insurance broker, Reich Insurance Group, to find out what you need to know about insurance if you're thinking of starting up a life sciences company.

Can you give us the "101" on insurance for life sciences businesses?

Although insurance isn't inherently complicated, when it comes to business insurance there are often multiple facets to consider; therefore, it is understandable why many companies – particularly start-ups – can get it wrong.

For a life sciences company, a normal business insurance policy – which covers a standard office – is not sufficient because there are unique risks in science, especially R&D and clinical trials. Consider the potential consequences of product spoilage, necessitating new product to be manufactured and the potential subsequent loss of business. If a company has, for example, been culturing something for five or six weeks and something happens – fire, flood, water damage or even accidental damage – the cost implications can be terrifying. How will you pay for the loss if you don't have the right insurance? And, for a small company, even a small loss can be financially devastating. It is unlikely investors will want to help out – and a small company won't have the cash available to remedy the situation. You need life science insurance that covers your offices, labs, manufacturing plants, and the cost of your R&D projects.

How should a company choose an insurer?

There are many brokers who can discuss your needs and help you find the best insurer, but you need to make sure they have life science expertise. As a broker, I would recommend finding a composite insurer that offers a full range of services, and picking someone with a recognizable name that has a strong presence in the life sciences insurance market. Don't opt for an insurer that is just dipping their toe into life sciences. Science and R&D are valuable, and you need to be sure that your insurer understands your business and the risk they are taking on. When something goes wrong and you need to make a claim, you need to know that your insurer can handle it and get you back on your feet as quickly as possible.

What are the common questions you receive? And how do queries from large and small companies differ?

Nine times out of ten, you'll find that all life sciences companies – regardless of size – have very similar insurance policies in place to cover the essential basics of the business. However, the largest companies will have additional "extras" in their policies because they may have specific needs and circumstances, such as more products on the market, larger supply chains spanning multiple continents, and multiple R&D projects, clinical trials and manufacturing sites. Larger companies also tend to have highly experienced individuals (and sometimes even an entire department) handling business admin aspects, such as insurance. Often, they have established cover in place and will want the same policy each time they renew, but they will also know what questions they should be asking to ensure they have the coverage they require: "Am I covered to send £100,000 worth of stock in a refrigerated container to Brazil?"

Small companies, on the other hand, may not be anywhere near having a commercial product and often seem unsure about what questions they should be asking.

What is the biggest misconception about insurance?

Easy: that a normal business policy is good enough to cover a life sciences business. Yes, it can cover your office, but it won't cover your R&D – which will be the most valuable aspect of your business.

Consider a scientist who has started up a business to work on a promising cancer treatment they have developed. At first, it may just be a one-man band – and they

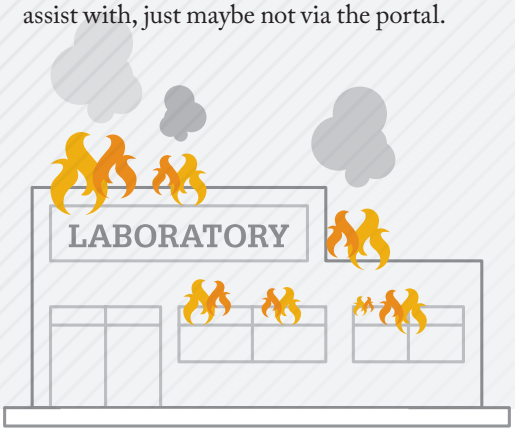
"Passion for science is essential but you need to make sure you have the right business coverage in place."

A Simpler System

Does anyone really enjoy shopping for insurance? Everyone wants the process to be as quick and painless as possible. You can buy home insurance easily online within just a few minutes, but business insurance can be trickier. The larger companies will know what they are doing, but start-ups can have a difficult time understanding how much coverage they need. In many countries, there is definitely a gap in the market for a simpler system to purchase life sciences business insurance, as the current processes are quite antiquated.

We've worked with many life sciences companies, so we know the basics that a policy must include and what premiums need to be, particularly for money-conscious small companies. We discussed this with a popular life sciences insurer in the UK (CNA Hardy), who gave us their underwriting criteria. In the UK, we recently launched an exclusive life sciences portal that can give an online quote for life sciences insurance – it's suitable for companies that are conducting research but do not have a commercial product on the market yet. You can simply go online, fill in your turnover band, number of employees, address, and other basic details, and receive a quote in minutes. You can also choose from different packages, but the basics are covered. For example, property damage up to £250,000, portable equipment anywhere in the world up to £30,000, flexible business interruption up to £30,000, employers' liability up to £10 million, product liability up to £5 million, professional indemnity up to £5 million and public liability up to £5 million. As we already have the underwriting criteria and have spoken with the insurer to develop the portal, the insurance costs are lower too.

The portal and the policies you can purchase from it are suitable for incubator businesses focused on R&D. Companies larger than an incubator will likely need additional coverage, which we can also assist with, just maybe not via the portal.



may be very inexperienced at running a business and what that involves. Passion for science is essential but you need to make sure you have the right business coverage in place.

Many start-ups simply want a cheap policy. It's not uncommon for someone to tell me they only want to pay something in the region of £150 ($180) per year, or that they have been paying a very low premium with another "perfect" insurance company that they want me to match. That low-cost insurance company was likely "perfect" because you didn't need to claim. With insurance, you are buying a piece of paper that you will file away somewhere. Often, you may not realize what exactly is written on that paper until something goes wrong! It is understandable for a life sciences company to want the majority of their cash to go on the science and to keep other business costs low, but a "cheap" policy is unlikely to cover a claim to the tune of £5 million...

I don't wish to scaremonger, but I am a broker and it is my job to look at the worst case "doom and gloom" scenarios (and, as we know from COVID-19, sometimes the worst-case scenario does happen). When you are looking for insurance, you need to ensure you are covered against the worst that could happen. If you are new to running a company and don't know what you should be asking, then the best thing you can do is to talk to your broker or insurer. They won't be a scientist and won't understand the technical nature of the work, but they will be experienced in risks. If you can get them to understand your business and what you are doing in layman's terms, then they will be able to understand what coverage you need.

Top Tips

- It's good to be money-conscious but R&D comes with large risks that insurers need to take on – so be prepared to pay more than you would to cover a standard office-based business.
- Pay attention to the wording of your policy schedule. Many people do not review until they have to claim – this is a mistake.
- If you are unsure, ask questions about hypothetical scenarios you want to be covered for.
- Be prepared for your insurer to ask questions; their job is to ensure you have the right coverage.

Pandemic Profiteering

Exploiting public concern, counterfeiters are using online platforms to sell a broad range of COVID-19 treatments

By Maryam Mahdi

As the industry has rushed to test existing licensed treatments for their potential efficacy against SARS-CoV-2, counterfeiters have jumped on the opportunity to make false claims and to sell fake medicines. Using online platforms like social media and e-commerce sites, fake developers tout their falsified products to consumers eager for solutions to the problem that has disrupted their lives.

The sale of fake pharmaceuticals has become such a significant issue that the World Customs Organization launched a group dedicated to real-time intelligence sharing on fake medical supplies and medicines to counter it (1). But counterfeiters are still managing to find ways of evading authorities and exploiting patients. Despite the recency of the pandemic, the FDA has already issued numerous warning letters for the marketing of unapproved COVID-19 therapies.

To find out more about the issue and how it can be addressed, we speak to Tim Mackey, Associate Professor and Director of Healthcare Research & Policy at UC San Diego, and Mike Isles, Director of the Alliance for Safe Online Pharmacy.

Why are counterfeit medicines so widespread?

Tim Mackey: It's an insidious trade, but where there is need and opportunity, fraudsters and criminals will take part. There are far fewer legitimate sources of prescription drugs on the Internet than there are fake or illegal ones, and counterfeiters take advantage of the fact that many patients don't have equitable access to legitimate medicines. This creates demand that can't be met for those who desperately need treatment – so criminals supply fake medicines to these communities for profit.

The opioid crisis, for example, created a void that cannot be filled through legitimate channels. Those suffering from substance abuse disorders seek out illegal channels to fulfil their habit. Some of these people will have encountered counterfeiters whose falsified opioid products are laced with fentanyl – and the consequence of such interactions can be fatal. In another case in the US, clinicians and drug purchasers were found to have bought counterfeit Avastin, a drug used to treat age-related macular degeneration, to sell for personal gain.

> *"It's an insidious trade, but where there is need and opportunity, fraudsters and criminals will take part."*

We're now seeing a similar pattern form with respect to COVID-19. The current climate has created prime conditions for fake drug developers to capitalize on patients' fears and their very real need for medicines, testing, and other forms of treatment. That's why the problem is so hard to solve.

Mike Isles: Illegal online pharmacy operations require little investment beyond a pill-pressing machine and some active ingredients (quite easily obtained, although not always present in the final product). The medicines can be typically manufactured in an unsanitary packaging plant (often just machinery in a garage) and advertised on a website – and criminals simply need to put a package in the post. Combined with variable regulations across borders and fairly lax penalties with the potential for huge profits, it's no wonder that criminals have chosen to focus on medicines. To tackle the issue, we need a comprehensive and coordinated response from everyone in the Internet ecosystem.

How has COVID-19 impacted the counterfeit medicine trade?

Mackey: In some ways, the pandemic may actually be negatively impacting certain illicit markets, because shipping counterfeit products to US customers (arguably the largest market for counterfeit drugs) is harder with fewer flights. The entire pharma industry is feeling the strain in terms of shipping and logistics – legitimate and counterfeit alike. However, it may also be helping grow the trade in online drug sourcing, as more people seek to source medicines online due to quarantine and stay at home measures. Further, criminals may now be "modernizing" their illicit supply chains by making them more digital, by tapping into available platforms, including the dark web.

Isles: I agree with Tim that it's becoming increasingly difficult to ship products and meet customer demand. But the problem isn't limited to a specific region; all countries suffer from similar situations. I was recently asked to give a live presentation for an OECD Worldwide webinar, "Illicit Trade at the time of the COVID-19 Crisis," that assessed how criminal activity has changed during the pandemic. COVID-19

has forced customs control authorities to change their priorities, and the labor shortages among law enforcement officials has helped criminals greatly to take up this new opportunity. Simply put, there are fewer people available to deal with counterfeiting. Coupled with the turmoil caused to legitimate supply chains because of drug shortages, it's obvious why there is an increase in opportunities for criminals to fill the space.

Which technologies show the greatest promise in tackling counterfeit drugs?

Mackey: There is a host of technologies that can help: analytical techniques for testing drugs, RFID for tracking drugs, blockchain to better secure the supply chain, and machine learning to identify potential illegal sellers from large volumes of data. However, all technologies have strengths and weaknesses. Blockchain systems, for example, need to interface and incorporate other anti-counterfeiting technologies. Although they offer approaches to cryptographically hash and distribute data from multiple parties, they are only as good as the data that goes into them. That's why fighting fake medicines requires an approach that integrates multiple forms of technology, robust surveillance, and smarter and more effective policy.

How can pharmaceutical companies protect patients from counterfeits?

Isles: The pharmaceutical industry is already doing a great deal to protect patients. For example, many established pharma companies belong to the Pharmaceutical Security Institute (PSI). Often, it's a pharma company's own security team that discovers counterfeiting or breaches in its supply chain – and they begin gathering evidence so that national police can follow up and connect with international law enforcement agencies.

In Europe, the Falsified Medicines Directive (FMD) ensures that all prescription packs are uniquely identifiable – a directive whose creation was in itself a significant development. FMD permits the sale of medicines via the Internet as long as the online entity (often an extension of a licensed pharmacy) is registered with the relevant authority. Depending on the category of medicine sold, various information is required. In the UK, for instance, prescription medicines can be bought online if the buyer can produce a prescription.

One solution that could complement the FMD is top-level domain names such as .pharmacy, which can be used by online pharmacies and sellers to verify their authenticity. The pharmacy domain name is regulated by the independent, non-profit National Association of Boards of Pharmacy and is proving successful in the US, with the big chains adopting it. I firmly believe that all EU member states should acquire a similar suffix word in their respective languages to create online "safe havens" for consumers.

We also need to educate the public about the dangers of counterfeit medicines and how readily available they are online. I strongly advocate for pharma companies to help educate the public and participate in endeavors that attempt to address counterfeit medicines.

Mackey: Pharmaceutical companies are in a position to ensure better safety of the global drug supply chain, including during pandemics. This will take some "coopetition", or collaboration between business competitors, on the basis of mutual benefit for protecting public health and also securing the integrity of their products. Organizations like PSI, initiatives like the NAPB's .pharmacy, and policy such as the FMD are also good examples of where coordination of stakeholders, innovative digital solutions, and governance around fake medicines is starting to take shape. Ultimately what is needed is a whole-of-sector approach, where pharmaceutical companies work directly with government regulators, technology platforms, and solution providers to take an active stance against having fake health products sold online. Developing coherence across policy instruments will also be necessary to incentivize this cooperation, including better leveraging the the US Drug Supply Chain Security Act, the MEDICRIME Convention, and ensuring technology innovation to fight counterfeit drugs is brought to bear.

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Cell Therapy 2.0

The first CAR T approvals were a major turning point for the cell therapy field. Now, companies are shifting their focus to the next wave: off-the-shelf (allogeneic) approaches, CAR T and TCR therapy for solid tumors, and combinations with immune checkpoint modulators

By Pippa Gledhill

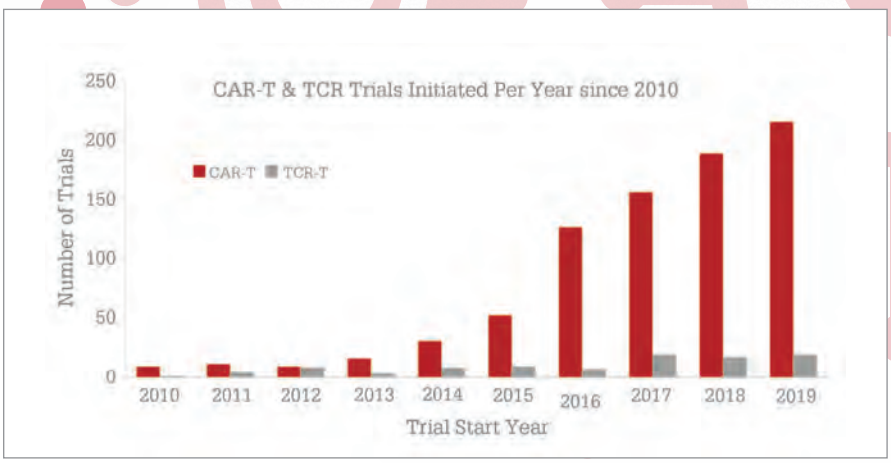


Figure 1. The number of trials evaluating CAR T or TCR therapies initiated per year since 2010. The compound annual growth rate for CAR T is 37.5 percent. *Source: Beacon Targeted Therapies, April 2020.*

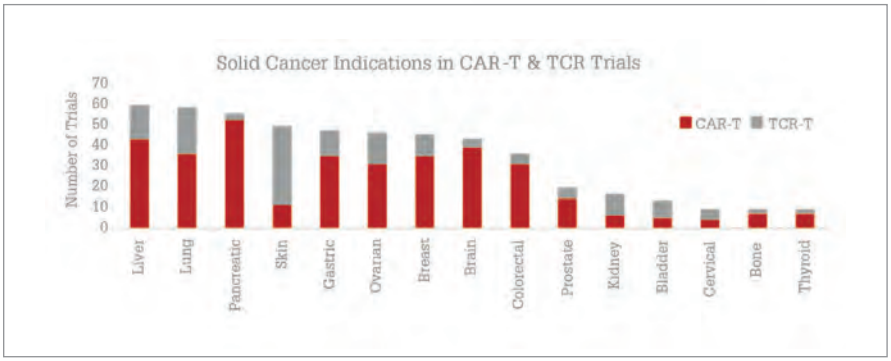


Figure 2. Solid tumor disease indications in trials evaluating CAR-T or TCR therapies. Source: Beacon Targeted Therapies, April 2020.

Back in 2012, a young girl named Emily Whitehead was discharged from hospital having entered complete remission from her life-threatening acute lymphoblastic leukaemia. Developed by Carl June and a crack team of scientists at the University of Pennsylvania, the treatment was made from Emily's own T cells modified to attack the cancer. In the eight years since this groundbreaking result, progress for modified cell therapies has been steady. Two CAR T therapies have been approved by the FDA and other regulators, with a further three poised for approval – and many more showing great promise in the clinic (see Table 1).

Following the approvals, investment piled into the sector. The result: 37 percent year-on-year growth in clinical trials (see Figure 1) to the point that the field now boasts well over 1000 trials across the globe. But after stunning early successes and billions of dollars of subsequent investment, there are still many unsolved challenges relating to the complexity of manipulating living cells. With issues from manufacturing and scalability to patient access and cost, the field is seeking approaches that boost the utility of modified cell therapies.

Advancing allogeneic therapies

Emily's treatment used her own cells, much like the other 480 autologous CAR T and TCR therapies currently in development. While offering a truly personalized approach, the deterioration of a sick patient during a lengthy manufacturing process can, in some cases, prevent treatment. Instead, creating modified cell therapies from allogeneic sources, such as from healthy donor blood, stem cells or cell lines, offers the ability to create an off-the-shelf therapy, which would allow patients to be treated faster and at a lower cost.

As of April 2020, Beacon Targeted Therapies reported 84 trials evaluating allogeneic CAR T and TCR therapies. Though the number is significantly lower than their autologous counterpart, the allogeneic space has grown four-fold in the past five years. More than 40 companies are working on these therapies with Allogene Therapeutics leading the way with UCART19, in terms of clinical advancement. To manage the potential of graft-versus-host-disease, TALEN gene editing technology can be used to knock out endogenous T cell receptors. Others, such as CRISPR Therapeutics, rely on alternate gene-editing technologies, whereas others avoid gene-editing completely; for example, Celyad uses a novel T cell receptor inhibiting molecule (TIM) in CYAD-101. Aside from T cells, the use of other immune cells that aren't MHC restricted, such as gamma delta T cells and natural killer cells, are increasingly popular options for off-the-shelf cell therapies.

Generally, clinical results are in the very early stages for allogeneic therapies. At the American Association for Cancer Research (AACR) meeting in April, Gracell Biotechnologies reported that 80 percent of patients with T cell acute lymphoblastic leukaemia achieved MRD negative complete response at day 28, after a single infusion of GC027 – an allogeneic CAR T.

Right now, opinions remain mixed as to whether the allogeneic approach will ultimately be successful. Naturally, more clinical evidence will be required but, until such data is shared, it seems likely that

CAR T and developer	*FDA/EMA approval status and disease indication*	*Target*	*Cell source*
Tisagenlecleucel (Kymriah) Novartis and University of Pennsylvania	August 2017: FDA approval for B-cell acute lymphoblastic leukaemia (ALL) May 2018: FDA approval for B-cell lymphoma August 2018: EMA approval for B-cell ALL and diffuse large B-cell lymphoma	CD19	Autologous
Axicabtagene ciloleucel (Yescarta) Kite, a Gilead Company	October 2017: FDA approval for large B-cell lymphoma August 2018: EMA approval for large B-cell lymphoma	CD19	Autologous
KTE-X19 Kite, a Gilead Company	December 2019: BLA submitted to FDA for mantle cell lymphoma January 2020: MAA under evaluation by EMA for mantle cell lymphoma February 2020: FDA grants priority review	CD19	Autologous
Lisocabtagene maraleucel BMS	December 2019: BLA submitted to FDA for large B-cell lymphoma February 2020: FDA grants priority review May 2020: FDA extends action data by 3 months for BLA	CD19	Autologous
Idecabtagene vicleucel (Bb2121) BMS & Bluebird Bio	March 2020: BLA submitted to FDA for multiple myeloma May 2020: Received FDA Refusal to File letter and EMA validates MAA	BCMA	Autologous

Table 1. CAR T therapies approved or awaiting approval, their disease indications, target and cell source.

both allogeneic and autologous therapies – each bringing their own advantages – are likely to coexist in the foreseeable future.

Tackling solid tumors

To date, CAR T therapies have only really proved successful in haematological malignancies. There are over 250 therapies in development against CD19, the target of preference for blood cancers. As the CD19 space becomes saturated and as the unmet need of solid tumors is recognized, an increasing number of developers are striving to create safe and effective therapies for solid malignancies. Several approaches are being explored with a view to not only identifying the right target antigen, but also to enable delivery to the hostile tumor microenvironment and infiltration into the tumor.

With an antigen-recognition capability that differs from antibodies, a unique selling point of TCR therapy has always been its potential to be highly effective in solid tumors. Of a total of 124 trials evaluating TCR therapies, 107 focus on the treatment of solid tumors. Adaptimmune, a frontrunner in the space, uses proprietary SPEAR T cells in a variety of disease indications from synovial sarcoma to liver cancer.

CAR T therapies are also making progress against solid tumors. Among the 248 CAR T trials in patients with solid tumors, the most targeted disease indications are pancreatic, liver and brain cancers (see Figure 2). A few strategies being used to overcome the barriers are local delivery methods (for example, in the T4 immunotherapy trial conducted at King's College London), the addition of soluble molecules targeting the tumor microenvironment (for example, IL-12 in Juno Therapeutics' JCAR020), and the targeting of multiple antigens, such as Celyad's CYAD-231. So far, results from small cohorts have been reported for 41 of the early phase trials. Other CAR-modified immune cell types, such as gamma delta T cells and natural killer cells, are also starting to emerge for the treatment of solid tumors, with 14 trials in the clinic and many more assets in preclinical development.

Again, more data, as well as an improved understanding of tumor biology, are necessary to fully understand the potential of modified cell therapies for the treatment of solid malignancies. However, driven by patient need and the commercial potential, it is likely that significant progress will be made in the solid tumor space in the coming years.

Creating combinations

Another important trend for CAR T and TCR therapies stems from harnessing the success of other therapeutic modalities in combination treatments. So far, therapeutic modalities explored in combination have ranged from oncolytic viruses to bispecific antibodies. The most explored is the use of CAR T alongside immune checkpoint modulators, with a variety of trials already in progress. To modulate the immunosuppressive tumor microenvironment, a checkpoint blocking antibody can either be independently administered alongside CAR T therapy, or built-in with an additional modification to allow in situ secretion. Autolus Therapeutics, for example, are currently evaluating their dual-targeted CAR T, AUTO3, as a standalone therapy and in combination with the checkpoint inhibitor pembrolizumab. On the other hand, the Shanghai Cell Therapy Research Institute has engineered CAR T cells to express PD-1 antibodies. This is a promising strategy and, as the field progresses, it will be exciting to uncover the best combinations.

For good reason, this is unlikely to be the first time you've heard about modified cell therapies, and certainly not the last. After the turning point of more approvals, and with increasingly advanced technologies and assets in development, the field is shifting focus towards the next wave of cell therapy. Whether they are allogeneic therapies, therapies targeting solid tumors, or combination therapies, we will undoubtedly see more researchers and patients joining Carl and Emily in the tale of adoptive cell therapy.

Pippa Gledhill is a Research Analyst at Beacon Targeted Therapies.

Going Global

Sitting Down With… Bobby Sheng, Chairman and CEO of Bora Pharmaceuticals, Taiwan

Did you always want to work in pharma?
My upbringing was a little unusual in that my father owned a pharmaceutical company in Taiwan. Every summer, I worked in the warehouse or the office, and I always felt that the work, in a small way, contributed to society by helping people live healthier lives. My father was keen for me to go into finance, so I studied economics at the University of California, Berkeley, where I grew up. Sadly, my father fell ill while I was at university and I had to take over the company when I was just 21.

How did you go about leading a company at such a young age?
When I took over, the company had an entrepreneurial feel, but had grown to over 200 employees. The first thing I did, with the help of family and consultants, was to create a more professional structure and set up an organizational chart. We tried to respect the board's governance as much as possible. It might sound daunting having to step in and lead a company at 21, but I had the help of some fantastic professionals – both those who had worked with my father and those we brought in.

You later branched out into other areas – including founding a record label…
First, we made sure that the company was stable. As Chairman, I worked closely with the CEO for almost a decade. But I was also interested in other industries, especially marketing, media, and tech. Our venture into tech was during the dot-com bubble and I rapidly gained experience with M&As: we merged five struggling companies into one successful company.

The label was something I wanted to check off the bucket list! I grew up in LA and always had a passion for music. I got into the business not as an artist, but as a producer/financier/executive. CD sales were declining, and pirating was widespread, so there was a demand for a label built specifically for digital music – especially in Asia. We founded Machi Entertainment. It was a great experience – and an invaluable one – despite being a world away from pharma, it has given me such diversity of experience that I can exercise across both the opportunities and challenges of our industry!

What made you re-focus your efforts on the pharmaceutical business?
Having dabbled in various industries, I was struck by how global the pharma industry is. Our pharma company, by contrast, was local to Taiwan. I remember thinking, "We haven't grown in a couple of years, but neither have our competitors." The market had reached maturity and the lightbulb moment for me was realizing that we had to go global or die. So, I gave everyone on the board a copy of "Who Moved My Cheese?", the well-known motivational business fable in which cheese is a metaphor for success, and told them, "The cheese has moved on!"

We needed to move into new areas, and contract manufacturing felt like the best fit for us. We had the capital and domain knowledge to succeed; plus, Taiwan has a rich history in the field, starting with PC cases, laptops, monitors, all the way through to iPhones – so it was almost a no-brainer…

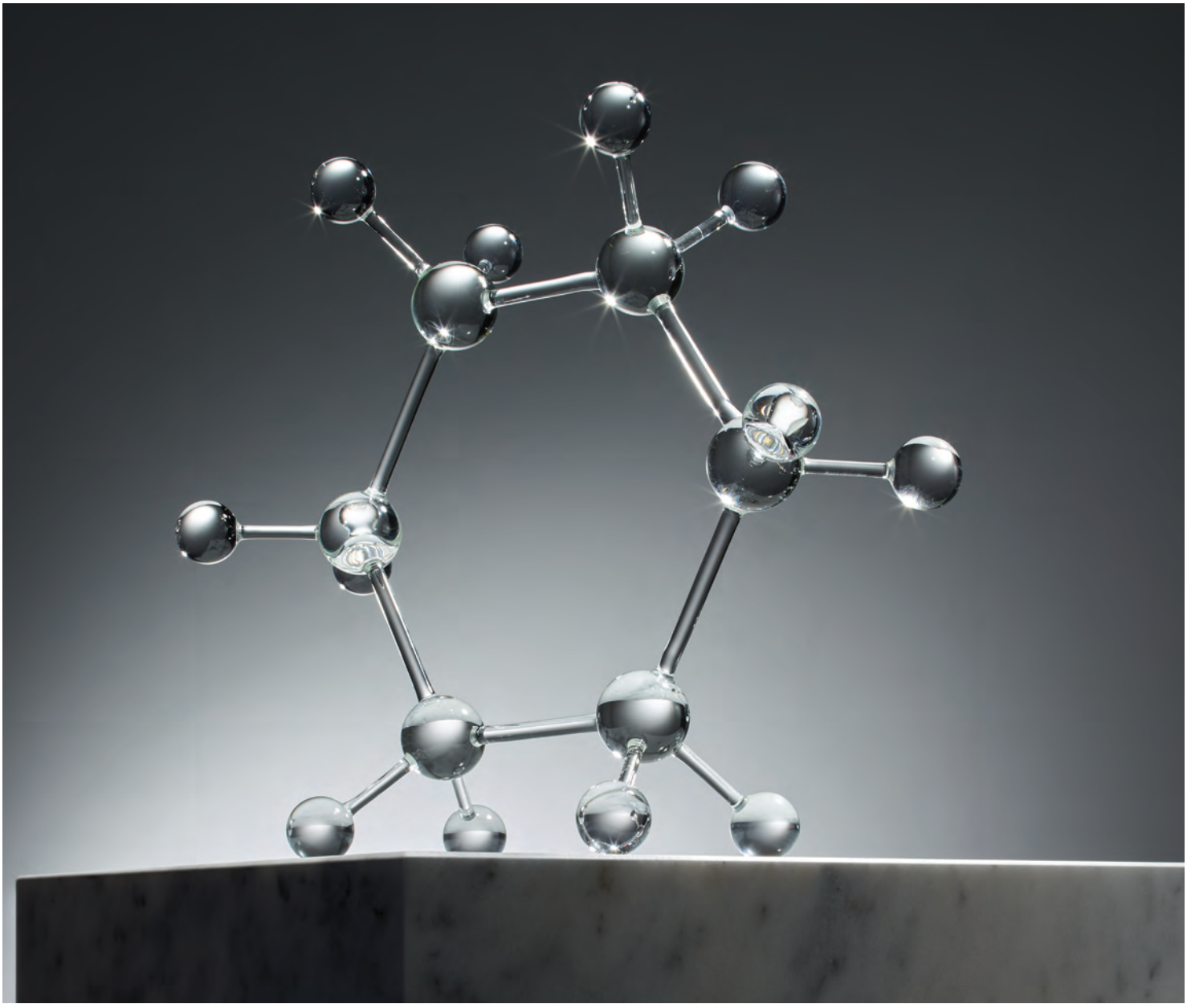
One of our longstanding partners happened to be selling a facility and asked if we wanted to take it over, so we did. It was our first foray into contract manufacturing and the business took off immediately. We decided to focus our efforts in this area and Bora Pharmaceuticals' contract services division was born.

What are your goals for Bora?
We're currently the largest CDMO in Taiwan, offering contract development and manufacturing services for complex oral solid dosage (OSD) drug products. We currently produce 12 percent of all drug products exported from Taiwan, but our ambitions are far more global still. We see a growing demand for large-scale, customer-centric contract manufacturers – not only in the growing biologics space, but also in the persistent pipeline of novel oral solid drug products.

Our strategy is organic growth in combination with acquisitions. For example, we are set to acquire GSK's facility in Ontario, Canada. The site produces around 50 different products for over 100 markets worldwide and employs 400 skilled manufacturing staff, whom we invited to join Bora as part of the transition. The deal is set to close later this year. We're very selective with our acquisitions and, with its highly skilled staff and the unique technology in place, we think the potential is huge. This acquisition in particular will expand our offering to include large-scale liquids and semi-solids manufacturing.

What has been the biggest challenge during your career?
Taking over at 21 in an industry where domain-specific knowledge is key was always going to be tough. The only thing I could do was manage from the heart, surround myself with people I could learn from, and study. From the age of about 23, I've read a book a month, including what feels like most of the management books out there, as well as plenty of pharma industry books too Either in books or through trial and error, I've learned a lot over the years, but you can never stop because there are always new challenges – even at 48.

Are there any books you recommend?
There are two books that I return to every three or four years: How to Win Friends and Influence People – a must-read for anyone who wants to be successful – and The Efficient Executive. Reading those books at different stages of my life has given me a fresh perspective on things and taught me a lot about myself.



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