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What *Are* Gene Therapies Anyway?

It's been great to see so many people talking about the science of vaccines, but some misconceptions arose – underscoring the importance of effective science communication and education

Over the course of the pandemic, it's been fascinating to watch what were once relatively obscure topics – fill and finish, production yields, and regulatory approval processes – all become front-page news. You might have even found yourself discussing vaccine technology with friends and family over dinner (or video chat). I certainly never thought I'd have so many conversations about mRNA (outside of work hours)...

As people book their vaccination slot, many want to know what an mRNA vaccine is and how it differs from a "regular" vaccine. They also want to know how these vaccines were approved so quickly and, most importantly, if they are truly safe. All fair questions. Perhaps more troublingly, the question of whether an mRNA vaccine is actually a gene therapy has cropped up – more than once.

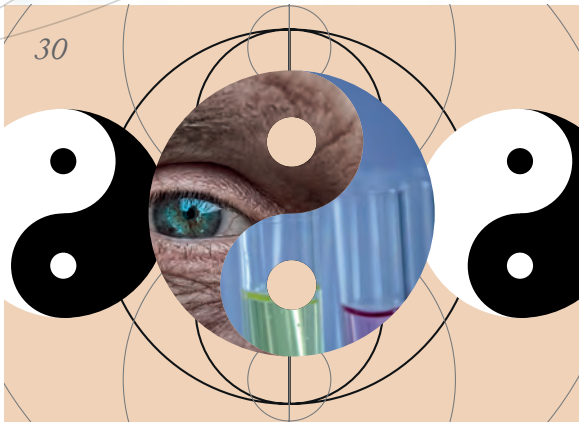
You will all know perfectly well that an mRNA vaccine isn't a gene therapy because, well, it doesn't do anything to your genes. But that logic requires some basic knowledge of what genes are and how they code for proteins – knowledge that a sizable proportion of the public sadly don't have.

Why should we care? If cell and gene therapies are to reach their full potential, more people – by which I mean potential patients and/or their carers – really need to understand what they are and how they work. But how many people really know the difference between gene therapy and gene editing? (Oscar Segurado helps us explain this to patients on page 40.) How many could define viral vector, viral infection, and vaccine? If the lines remain blurred, we might end up with a GMO-type situation where misconceptions threaten the success of the entire field. If individual patients don't understand their treatments, how can they give informed consent? And that's before we account for the spectre of unproven therapies, which can only feed the issue…

The situation isn't perilous. It's been great to see so many people sign up for trials and get vaccinated (check out page 46 for the inside story on the UK's vaccine strategy). In fact, there's every chance the pharma industry – including the gene therapy sector – could benefit from the positivity around clinical research and science more broadly. But let's get ahead of misconceptions by having the right conversations now.

James Strachan
Deputy Editor

Contents



On The Cover

Smart Container takes top spot in the 2020 Innovation Awards

Upfront

In My View

Feature

Best Practice

NextGen

Business

Sitting Down With

the Medicine Maker

ISSUE 77 - JULY 2021

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The Digital Advantage

How can pharma make the most of digital technologies? Experts shared their views at Veeva's Commercial and Medical Summit

Digital technologies are driving change at every stage of the pharmaceutical value chain. But are companies making the most of these technologies when it comes to maximizing their commercial presence? This was the main topic of conversation at this year's North American Summit, where industry leaders discussed the challenges and opportunities digital platforms provide.

Mamta Chhabra, Global Marketing Lead, Rare Diseases at UCB examined the evolution of media consumption among patients and the ways digital technologies can enhance direct-to-consumer marketing. In particular, she believes that pharma has to adapt to new ways of targeting consumers and measuring their data. "Digital is changing in the name of consumer privacy. Though this is good for patients [...] it's going to be critical to have access to first-party data (direct from the audience) that can be connected to offline health information."

GSK's VP, Global Pharma Marketing Operations, Raakhi Sippy, shared her views on the importance of digital transformation. Prior to adopting digital, GSK worked with many agency partners – affecting their ability to create a scalable, intelligent content dissemination model. They have now consolidated their operations and adopted a single platform for their commercial arm. "A unified approach is essential to pharmaceutical operations. It's really the backbone of data gathering, analytics, and measuring the effectiveness of content at the consumer level," she said.

Another important area for consideration is data architecture. Raakhi said, "In pharma, we have heaps of data but, if it isn't structured, it becomes meaningless." By creating appropriate channels for this information, tangible insights can be gathered to help inform commercial decisions.

Pooja Ojala, VP, Commercial Content at Veeva provided further insight into what scalability means from a marketing perspective. "Operating models need to evolve with businesses. But scale up can mean many different things, including the growth of marketing channels (ways of bringing products to the consumer's attention), spread across geographies, and the types of content produced," she said. "Thinking about tech partnerships, agencies and operating models is essential."

INFOGRAPHIC

Security Threat

Report analyzes pharma's vulnerability to cybersecurity attacks

12.2% of pharma companies are highly susceptible to ransomware attacks

47% have more than 1,000 leaked credentials on the deep web

Small and medium-sized companies are targeted in **73%** of ransomware attacks

Source:
Black Kite, "The 2021 Ransonware Risk Pulse: Pharmaceutical Manufacturing" (2021). Available at https://bit.ly/3cMbLX0.

BUSINESS-IN-BRIEF

Identifying new therapies, enhancing medicines access, and newly approved brand names… What's new in business?

- With the aim of approving new COVID-19 therapeutics before the end of 2021, the European Commission has identified five monoclonal antibodies with the potential to treat the condition. Three of the candidates are already expected to receive marketing authorization in October. "Vaccination is progressing at an increasing speed, however, the virus will not disappear and patients will need safe and effective treatments to reduce the burden of COVID-19," said Stella Kyriakides, Commissioner for Health and Food Safety, in a statement.
- Johnson & Johnson has reached a settlement agreement worth US$230 million with the state of New York, putting an end to its hotly anticipated opioid trial, which was expected to begin this June. In a statement, the pharma company claimed that the deal was "not an admission of liability or wrongdoing." However, as part of the agreement, Johnson and Johnson will discontinue its production of opioid drug products.

- The EMA has approved Moderna's brand-name application for its COVID-19 vaccine. Coined Spikevax in Europe, the vaccine cannot yet receive similar approval in the US as it has only been approved for emergency use authorization.
- In a move to help improve medicine access across the US, Walmart has pledged to offer its customers insulin at discounted prices with the support of Novo Nordisk. The retail corporation intends to sell a private label insulin analog, ReliOn NovoLog, at $72.88 per vial or $85.88 per box of injectable pens – saving customers up to 75 percent off the cash price of branded insulin products.

Tough Decisions

How does the FDA plan to increase COVID-19 vaccine availability?

The FDA has granted emergency use authorization to Janssen for two batches of its vaccine produced at an Emergent Biosolutions plant (1). In May 2021, the plant came under scrutiny for contaminating the active ingredient of Janssen's vaccine with ingredients from AstraZeneca's product. But, after a lengthy review of Emergent's facility, record, and quality testing procedures, the FDA decided that the batches were safe for use domestically or abroad. Several other batches produced at Emergent's Baltimore facility are currently under review.

"This review has been taking place while Emergent BioSolutions prepares to resume manufacturing operations with corrective actions to ensure compliance with the FDA's current good manufacturing practice requirements," said Peter Marks, Director of the FDA's Center for Biologics Evaluation and Research in a statement (1). He also added that the expiration date of Janssen's vaccine would be extended to reflect data submitted by the company.

Reference

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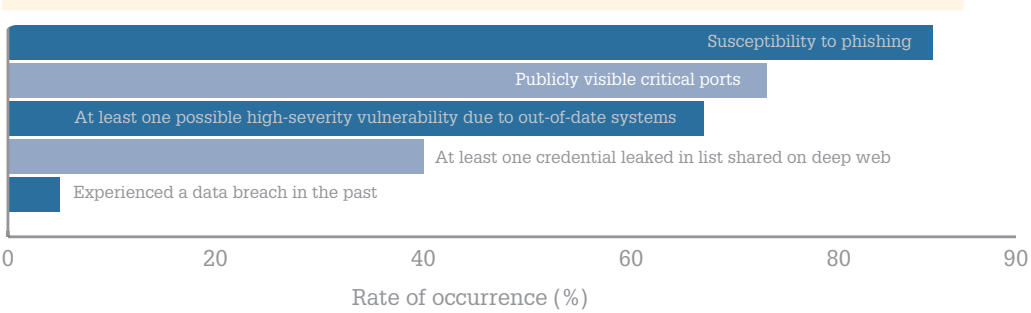
In 2020, US healthcare and pharma companies spent **$20.8 billion** to address **92** ransomware attacks

Most impactful ransomware issues for pharma vendors



Just Press Print

Can decentralized additive manufacturing bring customized medicines to targeted patient groups?

Researchers at the University of East Anglia (UEA) and Loughborough University, UK, have developed an additive manufacturing technique that allows for the production of highly porous medicines with tuneable release profiles. The team believes that the approach could be used to develop customized drugs for patients at the point of care (1).

"Though 3D printers can't replace conventional large-scale manufacturing methods, such as tableting, their flexibility, small footprint, and portability make them well suited for small batch production of medications for targeted patient groups with specific clinical needs," says Sheng Qi, a reader at UEA. The new 3D printing method used by the UEA researchers relies on hot melt droplet deposition to print medicines. In contrast to the traditional fused deposition modeling method that relies on the continuous deposition of "roads" of materials, hot melt droplet deposition 3D printing builds the 3D structure by fusing tiny droplets of molten materials together. This allows for the printing of highly porous structures with good precision. By manipulating the size of pores within tablets, the 3D printing approach can produce small batches of solid dosage forms that are capable of regulating drug release depending on the patient's needs.

Qi explains that the technique could be particularly beneficial for patients with polypharmacy, as the printer also allows for drug combinations to be developed. "By using printed tablets, elderly patients, as well as those living with chronic conditions, all stand to gain as they can access maximal drug benefit with minimal side effects and reduce their burden of taking the medicine," she says.

The team is collaborating with industry professionals and the UK's National Health Service to translate their research from academia to healthcare and pharmaceutical settings, which will include rethinking supply chains. "A new type of supply chain network is being developed to suit small batch and point-of-care manufacturing," says Qi. "It's exciting to see how the role of traditional medicine manufacturers will change and how additive manufacturing will influence the future of drug development."

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A Year Like No Other

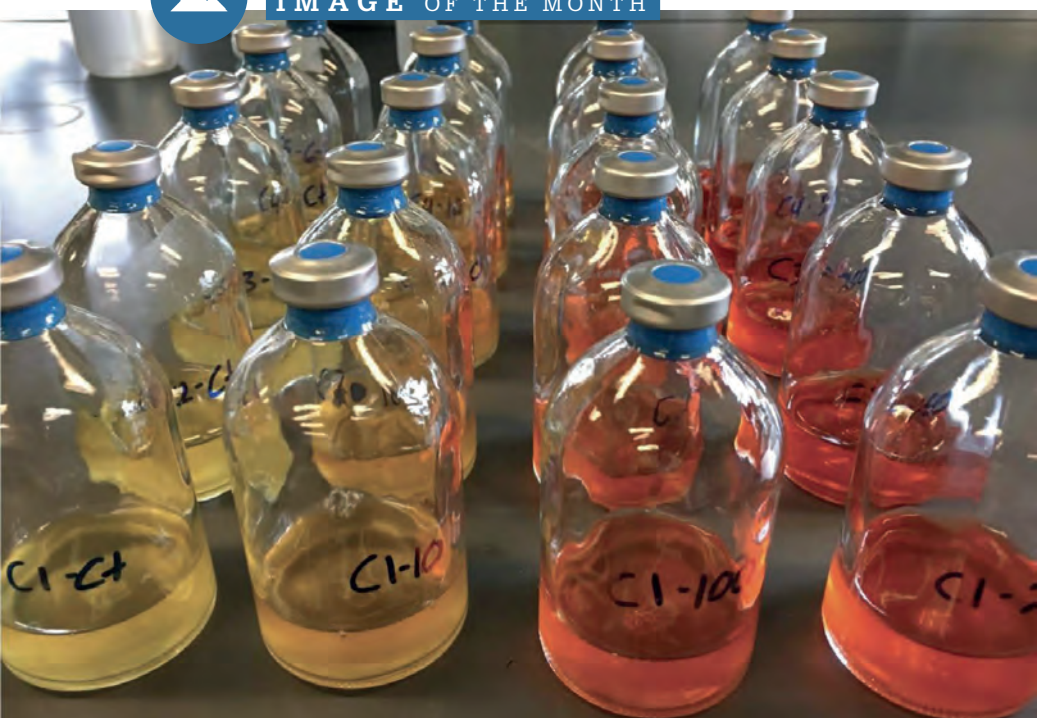
Showcasing the EMA's achievements in 2020

The EMA has a long history of providing guidance and support to European pharmaceutical companies. But how did the agency fare in 2020? In a June 2021 report, the European regulator shared details of its approach to managing key issues such as the COVID-19 pandemic and the threat of antimicrobial resistance.

In the document's foreword, Christa Wirthumer-Hoche, Chair of the EMA Management Board, praised the agency for its ability to adapt to change. She said, "The pandemic started just as EMA was completing its relocation to the Netherlands and setting up in its new office in Amsterdam. The agency swiftly adapted its activities and processes to ensure a rapid response to the pandemic whilst maintaining their core activities to protect public health."

To find out more about the EMA's achievements in 2020, visit https://bit.ly/3zyQslC

IMAGE OF THE MONTH



On Guard

Researchers at Northwestern University have developed mock gut communities, which can determine the organisms in the microbiome that are capable of preventing the harmful effects of chemotherapy drugs on "good" bacteria.

Credit: Northwestern University

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

QUOTE of the month

"Handing needy countries a recipe book without the ingredients, safeguards, and sizable workforce needed will not help people waiting for the vaccine. Handing them the blueprint to construct a kitchen that – in optimal conditions – can take a year to build will not help us stop the emergence of dangerous new COVID variants."

Michelle McMurry-Heath, president and CEO of the Biotechnology Innovation Organization on the Biden Administration's support of the TRIPPS vaccine waiver. https://bit.ly/3zes315

Advancing Biotech

Gene therapy company wins 2021 Advance Biotech Grant

VectorY, a gene therapy company based in the Netherlands, has been selected to receive Merck's 2021 Advance Biotech Grant for its adeno-associated virus platform that can help improve outcomes for patients with muscular and neurodegenerative disorders. As part of the grant, VectorY will also have access to Merck's products and consultation.

"Winning the grant is invaluable in ensuring the continued success of our gene therapy programs," says the company's Chief Operating Officer Tony Newcombe. "VectorY is currently in the process of setting up in-house R&D infrastructure and we intend to include production capabilities to deliver suspension-based AAV viral vector manufacturing up to 2000 L for both clinical and commercial supply."

Merck launched the Advance Biotech Grant in 2014 to seek out promising biotechs and support their product journeys from discovery through to manufacturing. The grant program is open to drug developers in Europe, North America, and Asia and runs for six months in each region before moving to the next.

To find out more, visit https://bit.ly/3gw4VHm

Take Care of Yourself!

COVID-19, Brexit, and the digital challenge – unpacking the unpredictable demand for over-the-counter medicines

"Take care of yourself" – four friendly words that have found more sincere meaning over the last 18 months. When we look back at the COVID-19 pandemic years from now, we will most likely acknowledge the healthcare and pharmaceutical sectors as the heroes of the hour. The novel therapies, access programs, and rapid reaction to change were hallmarks of their response. But we shouldn't forget the role played within the sector by the over-the-counter (OTC) industry in helping to protect patients – especially as people were asked to manage their conditions following stay-at-home orders issued by governments.

As time has progressed, new challenges have arisen for OTC developers. Current market uncertainty means that they must remain ever-vigilant while working through long-standing challenges.

Here, we speak to Michelle Riddalls, Chief Executive Officer of the Proprietary Association of Great Britain (PAGB) – the UK trade organization for manufacturers of OTC medicines, self care products, and food supplements – about the issues the industry faces and what the future holds for their products.

What influence has COVID-19 had on the OTC market?

The pandemic has altered the dynamics of the OTC world. Last March, the industry saw a significant uptick in sales. People were fearful about the situation, so they bought more essential items, including self-care products like painkillers and cold and cough medicines. From a customer perspective, it was a matter of wellbeing and protecting their immunity. In a survey we conducted last year, 69 percent of people who wouldn't have considered self-care as a first option before the pandemic said they would do so in the future. Staying at home and self-monitoring is our ultimate self-care message and so it's interesting that people are now seeing the value in it.

This shift in mindset has highlighted the importance of OTC to the wider community. Often, such medicines aren't viewed as lifesaving or critical, but the panic-buying that we saw provided insights into public behavior and proved OTCs to be an integral part of the industry.

What about the challenges?

Social distancing and lockdowns resulted in a nonexistent cold and flu season, which had obvious ramifications for OTC manufacturers. At the start of the pandemic, there was a surge in the use of cold and flu products, but we're now experiencing a lull. The experience has left a lingering question: will we experience a similar situation as this year draws to a close? To compensate for uncertainty over changing patterns of seasonal infection, many companies – especially those that are heavily reliant on cold and flu products – are reconsidering their current drug portfolio.

Brexit is a well-established issue for OTC manufacturers in the UK and Europe. How are they coping?

I've been living and breathing Brexit for several years now. There are several issues that still need to be addressed. One example is the additional licensing required to move products from the UK into Europe. Prior to joining PAGB, I was heavily involved in industry Brexit planning. My colleagues and I knew that British drugs, both branded and generic, would be subject to batch and QC testing before their release and that many referential management services (used to support regulatory activities in the EU

region) would need to switch to decentralized procedures and obtain new licenses.

The UK was a major marketing authorization holder for centralized procedures, which meant that new manufacturing facilities had to be scouted out to accommodate drug development in the EU. Also, many countries are reliant on UK licenses for products; across the Middle East and Africa, companies have had to consider the ramifications of Brexit on logistics. How will products reach their target destinations with new barriers in place?

Fortunately, the OTC sector, unlike other segments of industry, hasn't faced issues with supply continuity. But we all have hurdles to overcome when it comes to Northern Ireland. As an organization, PAGB has had a great deal of input in conversation on the topic last year. One of the first things I did as CEO was to raise concerns over how products would reach consumers in Northern Ireland. We provided a great deal of data and produced case studies, which helped feed into Brexit negotiations. That led to a year-long delay in the introduction of the new arrangements, which was very welcome, but there are still things that we need to examine to help smooth out the process of supplying medicines to Northern Ireland. As we all know, there are no easy solutions to this challenge.

Can digital tools help?

Digitalization is an exciting new area for PAGB. When I joined the organization, everyone was talking about digital but didn't really understand what it meant or how it could be applied. However, because of my industry experience, I think that I had a wider understanding of what digital tools could do for our members. Together with my colleagues, I developed different work streams that would help support our membership. For example, we are looking at how different apps can support people in using over-the-counter medicines and medical devices, and how they can improve people's understanding of symptoms and health conditions. We're also gathering real-world evidence for clearer insights into the OTC market and looking at the ways we can improve our relationship with regulatory bodies. Our members can now use a developer toolkit to search for and use appropriate claims in their digital advertising strategies. The toolkit also helps in expediting the approval process for packaging by ensuring that accurate information is included on drug labels provided to consumers and healthcare professionals.

What are your future plans?

We launched a new strategy in 2018 that outlines the organization's goals between 2020 and 2024. Our main objectives are to encourage self-regulation and create a comprehensive self-care strategy within the UK. We want to be recognized within the industry as an expert voice on OTCs. At the top of our agenda? Supporting our members with their activities as they continue to navigate the challenges presented by Brexit and COVID-19 – as well as the increased need for more robust digital toolkits.

Another goal is to make the government more aware of our role. If more patients are able to self-manage, healthcare services will benefit. We all know the strain our hospitals and health services have been under as a result of the pandemic; if we can extend our reach, we can help support different stakeholders invested in the wellbeing of patients.

Though there's always more to be done, we're proud of our achievements so far. For a small organization, we have a loud voice – one that we've used willingly (and will continue to use) through these challenging times! In short, we'll do whatever we can to help support OTC manufacturers across the industry.

In My View

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

COVID-19's Digital Legacy

Efficient data management is critical to meet the demand for fast drug development – especially today

By Claire Hill, Head of Strategic Marketing, IDBS

Developing drugs and therapeutics is a complex and expensive undertaking that, under normal circumstances, takes upwards of US$1 billion and a decade or more across the entire development lifecycle. But, during a pandemic, we simply don't have a lot of time to play with. Companies involved in COVID-19 vaccine development have had to deviate from the standard ways of doing business to enhance efficiencies, improve collaboration, and reduce the time it traditionally takes to bring a solution to market. Increasingly, this means establishing new systems, technologies, and strategies, which capitalize on a company's most important asset: data.

Managing mountains of data, whether you're a contract development and manufacturing organization (CDMO) or a large pharma company, is no easy feat – and revamping how those data are handled can shave significant time off the R&D process. Part of the problem is that many drug development firms are stuck using legacy systems and outdated methods of data capture, not to mention inefficient collaboration between teams and organizations. These issues presented large enough hurdles to establishing workflows before the pandemic, but COVID-19 has exposed them as more serious hindrances, squandering opportunities for higher throughput of viable – and lifesaving – products.

Working from home became the norm during lockdowns around the globe. If we were heavily reliant on technology before, it was nothing compared to our needs now. Technology has seeped into every aspect of our lives – shopping, work, healthcare, and social contact. It has evolved from a complement to sustenance – and the life sciences industry is no different.

Across the globe, there's an increasing need for collaboration between R&D and manufacturing teams to help mitigate impending capacity shortages. Viral vectors, a key component of gene therapies, were already in short supply and now increased demand from AstraZeneca and Johnson & Johnson's recombinant vector vaccines is compounding this capacity crunch (1). COVID-19 vaccines and therapeutics are also likely to cause more general biomanufacturing capacity challenges (2). Limited by the constraints of the current situation, many drug development companies are embracing the benefits of technology, for collaborating with colleagues and moving R&D projects forward while simultaneously building up capacity.

Scientists want to get on with their work, especially in these times – but when it comes to meeting regulatory requirements, and ensuring experimental data is collated and recorded accurately, the administrative burden can be staggering. This is especially true for labs using outdated methods of data capture. Notebooks, study binders, and Excel spreadsheets are prone to human error. Even when you're using laboratory information management systems (LIMS), some data may still need to be captured manually, especially administrative information, for compliance reasons. Research even suggests that up to 50 days in an R&D scientist's work year is spent recording data manually – which explains why up to 20 percent of development work

must be repeated due to data integrity problems (3).

Companies that have made the leap to digital are generally moving faster than those using legacy systems to capture, organize, and store data. The combination of automation and best industry practice built right into software significantly reduces human error, which reduces the need for repetition and saves time.

A nice example of how streamlining data management has real-world effects is in the US-based biotech company Moderna. It was one of the first to develop and manufacture a vaccine against SARS CoV-2 and commenced clinical trials in mid-March 2020. As the virus' genetic sequences had only been published 63 days before trials began, Moderna's agility was nearly unprecedented.

hough SARS CoV-2 is a novel coronavirus, Moderna had previously worked with partners on the Middle Eastern Respiratory Syndrome coronavirus, MERS-COV. While that vaccine had only reached the early research phase, Moderna has said that the data captured and stored from that study was invaluable to their swift response to SARS-CoV-2.

For one, it provided deep insight into the mRNA-based vaccine, which shortened the research timeline. For another, simply having all the data and experimental information from the MERS outbreak at their disposal made it possible for scientists to apply that knowledge to the current pandemic. Imagine the potential for scientific breakthroughs – and preparation for the next pandemic – if this were the norm.

Herein lies the value of scientific informatics software: it can organize and contextualize R&D data, cutting weeks or months off drug development and obviating the need for re-work. What's needed to consistently achieve this across the industry is an entirely new category of software; Biopharmaceutical Lifecycle Management (BPLM), an operational foundation for drug development that creates a comprehensive data backbone across the development lifecycle. The key to BPLM is ensuring valuable data is automatically captured in context at the point of execution, ensuring data integrity and making it easier to gain insight from collective experience. Time savings and increased efficiencies like these could ensure patients have access to life-saving therapies that much faster, without compromising safety or quality.

But data capture is only one area of lab life that needs improvement. As we've seen from the unprecedented level of collaboration among biotech companies during the current pandemic, collaboration itself should be a new normal. While collaboration doesn't demand a cloud environment, cloud integrated technology and applications are helping companies build in efficiencies at the foundation. Cloud technology is a key enabler of more holistic end-to-end digital workflows which can be rolled out quickly and scaled up or down on demand, allowing more fluid collaboration across teams and reducing the burden on researchers.

Bringing together the combined expertise in R&D, manufacturing, and supply chain management across all organizations involved in vaccine and drug development could make all the difference for current and future global health challenges.

As smart data collection and collaboration are key ingredients, communication is also integral. Drug development rarely occurs in a single location. Teams are strewn not only across multiple labs, but across cities and countries – but need to work collaboratively on many levels using a variety of systems. Even if labs use the same technology and instrumentation in their daily runs, without a common method of collating, recording, and sharing their data, this doesn't mean much – errors and inefficiencies are bound to occur. Just as human error can derail progress in recording and analyzing data, ineffective collaboration across teams and organizations can do the same.

And today, even as labs and office are re-opening, there is still a significant percentage of people working remotely which means the right tools are even more essential in effective communication. Data can be shared in ways that are convenient but imprudent – emails can get lost and spreadsheets altered, both of which undermine integrity. Data strategy must therefore be at the forefront when it comes to setting up business objectives for R&D teams.

As COVID-19 continues to be a threat throughout the world, partnerships and collaborations across the biopharma industry are helping to break down silos which have historically slowed progress (4). Achieving efficiencies was always important; it's even more important now. The right combination of effective data tools, technologies, and management is clearly a very smart place to start.

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Don't Break My Strands

CRISPR-engineered cell therapies with multiple gene knockouts could be limited by double-strand breaks

By Emily M. Anderson, Principal Scientist at Horizon Discovery, a PerkinElmer Company, UK

Ex vivo gene editing and cell therapy have the potential to revolutionize how we treat both rare and common diseases. The initial success of cell-based therapeutics for the treatment of blood cancers has set the ball rolling, but challenges, such as the immunosuppressive environment of solid tumors, have yet to be overcome. Another promising technology, CRISPR-Cas9-mediated gene editing, is poised to meet these challenges head-on, but not without a few bumps (or breaks) in the road.

CRISPR-Cas9 has a definite advantage over previous forms of gene editing technologies such as meganucleases, engineered zinc finger proteins, or TALENs. Although each of these technologies requires redesign and reconfiguration of a protein to target different sequences of DNA, CRISPR system effector nucleases, such as Cas9, use a small strand of RNA to recognize sequences of DNA – meaning that the same protein can be easily configured to target new DNA sequences by loading a different targeting RNA, known as the CRISPR RNA or crRNA. This new technology democratized the field of gene editing and allowed for high-throughput synthesis and testing of CRISPR editing technology against many human genes in academic and preclinical settings, with an eye to eventual therapeutic applications.

However, we should take a step back and acknowledge that CRISPR-Cas9 and other gene editing technologies have been somewhat overhyped as precision gene editors. In reality, their magic extends only as far as the site-directed cutting of a specific sequence of DNA. This is no small feat, because the human genome contains billions of DNA base pairs, requiring exquisite specificity to target such a needle in a haystack. However, the phenomenon of gene editing comes about through the cell's repair mechanisms, which are activated as a result of a DNA double-strand break (DSB) introduced by Cas9. In general, the dominant pathways for repair involve either non-homologous end joining (NHEJ) or homology-directed repair using a template. NHEJ induced by a CRISPR-Cas9 cut is often imperfect, leading to small insertions and deletions at the repair site that can disrupt and therefore knock out the gene.

Gene knockout with CRISPR-Cas9 has made it to clinical trials, for instance for the treatment of blood disorders such as sickle cell anemia and beta-thalassemia (1). In this case, much like adoptive T cell therapies for cancer, the edit is made ex vivo and the therapeutic cells are infused back into the patient. However, for cancer immunotherapy, it is likely that more than one gene knockout will be required to augment the properties of the immune cell used for treatment. It is here that the DSBs caused by gene editing could really have an impact.

DSBs are the most cytotoxic lesions naturally occurring in DNA and have the potential to lead to cell death or chromosomal translocations, in which segments of two different chromosomes join aberrantly. Notably, introducing multiple DSBs at once with CRISPR-Cas9 increases the risk of translocations. The number of possible reciprocal balanced translocations (T) increase quadratically with the number of DSBs (N): $T=N(N-1)$ or $T=N^2-N$.

However, translocations can take many forms. They can be classified as balanced, reciprocal translocations, Robertsonian translocations, inversions, de novo translocations, sex chromosome rearrangements, and translocations

"Will novel technologies such as base editing take the lead in overcoming this reliance on DSBs and offering safer multiplex editing of the genome?"

involving more than two chromosomes. Add to this the possibility that each crRNA used for targeting one site has the potential for off-target effects, meaning that the crRNA could imperfectly pair with other target sites in the genome and cause a break at some frequency (hopefully lower than at the intended target site). The potential for translocations caused by on- and off-target DSBs increases quadratically, so the risks of this strategy mount precipitously. Although most rearrangements have detrimental effects for cellular survival, single events have the potential for a clonal advantage and may result in abnormal cellular proliferation, which could affect the safety profile of the engineered cells or even lead back to cancer.

As an example, a recent clinical trial involving CRISPR-Cas9 knockout of several T cell targets in a TCR therapy model (2) indicated that in general, over many months in several patients with refractory advanced or metastatic cancers, the treatment was safe and well tolerated; however, about four percent of the infused cells contained genome rearrangements. It remains to be seen how improvements in the technology will lead to greater knockout efficiency of multiple genes while reducing this translocation risk for the number and identity of genes targeted.

One way to alleviate the potential danger multiple CRISPR-Cas9 gene knockouts pose to immunotherapy involves gene knockout without introducing a DSB. Base editors have this ability because they make use of a nickase version of Cas9 tethered to a deaminase enzyme. The Cas-targeted deaminase acts on cytosine or adenine bases to convert them to thymine or guanine, respectively, when the deaminated base is repaired via the mismatch repair pathway in the cell. Instead of relying on imperfect NHEJ repair to disrupt gene function, mismatch repair can introduce stop codons or disrupt splice sites, which leads to functional disruption or knockout of a gene (3) without introducing DSBs.

There is little doubt that multiple gene engineering holds great promise to improve the field of cell therapy, but the goal of efficacy balanced with safety requires a cautious approach. Newer generations of gene editing technologies could very well break the "multigene edit barrier" without breaking the system by incurring too many DSBs. Will novel technologies such as base editing take the lead in overcoming this reliance on DSBs and offering safer multiplex editing of the genome? It is with much anticipation that researchers look to see these developments in the clinic.

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Inclusive Drug Development

Gender diversity in pharma: better health for all requires medicines that are made for all

By Ann Taylor, Chief Medical Officer at AstraZeneca

The scope of opportunity to improve inequities in drug development is vast. Race, geography, sex, gender, and other disparities across the development cycle – including lagging trust among patients, provider knowledge, time constraints, and physical and financial barriers to participation – are areas where we know industry must do better. But the lack of female representation in clinical trials impairs the very foundation upon which the discovery and development of safe, effective medicines is built.

To understand how medicines work in the populations we serve, we must make every step in the drug development process more inclusive, starting with appreciating sex (female and male) as a biological variable in drug development (while also acknowledging there is more to consider about how gender influences patient outcomes). There are certain situations where chromosomes don't predict or aren't aligned with identity or status, yet still influence drug effectiveness. These are important distinctions to consider in evaluating the safety and effectiveness of medicines. Achieving sex parity in drug development requires bringing talented individuals to industry who reflect the diversity of our patient populations – and this pipeline begins with quality STEM education.

As an endocrinologist, the way hormones impact disease expression, response, or drug effects is always at the forefront of my mind. A greater appreciation of the importance of sex as a biological variable in drug development will shift how we study the populations we seek to treat, from preclinical through to post-marketing. For several reasons – some more valid than others – the drug development process has historically prioritized understanding how males react to medicines. But the differences in how females perceive illness, experience side effects, and respond to medicines are critical to understanding how safe and effective a given medicine is for more than half of the population.

Historically, women's exclusion from scientific research started with preclinical animal studies (1), which set the course for underrepresentation of females throughout the drug development process. It wasn't until 1993 that the FDA reversed its recommendation to exclude women with childbearing potential from early clinical studies. Nearly 30 years on, females (particularly of childbearing age) are under-enrolled in phase I and II studies (2). More diverse teams can come up with solutions to allow for better inclusion of women of childbearing age, including contraceptive coverage, childcare solutions, and more; simple solutions that, if considered upfront, can create a more complete picture of medicines' safety and effectiveness. Failure to have a representative pool of participants enrolled in clinical trials ends up harming patients when medications reach the market. In some instances, up to 80 percent of drug recalls are due to unacceptable health risks and adverse events reported by women (3).

Addressing these biases and structural disparities is not a program or a project. It requires fundamentally reshaping our work, our thinking, our talent, and our investments. We can start by accelerating our efforts to increase diversity among the teams bringing medicines to market. Teams that are diverse – among sexes or genders, but also in perspectives, education, geography, race, and ethnicity – will invariably do a better job developing and commercializing medicines, with the patient always central to the process. Diversity in pharmaceutical development teams increases the likelihood that someone on the team has experience relevant to the patient population in the study. For example, diverse teams with an understanding of issues for trans men may help the team more carefully consider the ways to manage the hormones and potential response of a trans man, including understanding their risk (albeit small) of pregnancy.

Creating a pipeline of talent to fill the tables that welcome diversity begins with investing in STEM education. Women drop out of STEM at a young age – starting in middle school and increasing throughout high school and university (4). The same attrition of women into leadership roles is true in industry (5). Conscious effort can help slow this attrition. For example, at AstraZeneca, we have 45.5 percent women in leadership positions with the goal of 50 percent by 2022. Achieving more balanced teams makes our products, and our processes, better. Similarly, our commitment to supporting the next generation of STEM talent with intentional, accessible mentoring, modeling, and resources is an early investment in the potential of future innovative drug developers.

Science needs diversity – in our teams, in the populations we study, in our thinking, and in the approaches we take. Corporate commitments to improving female representation and investing programs to support women in leadership positions should be the rule, not the exception. If our ultimate goals are to develop medicines that truly address people's unmet needs, then we must think about who these people are at every stage. The best way to do that is to ensure that the groups of people in charge of making medicines better reflect the populations we seek to treat.

Diversity in the drug development process, and diversity in workforces broadly, is not a "nice to do." It's a business – and ethical – imperative to enable the

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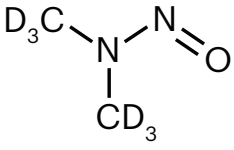
Deutero N-Nitrosodimethylamine RS (NDMA-d6)

Catalog #: 1175800

Category: USP Internal RS

Chemical Name: *N*-(Methyl-d_3)-*N*-nitrosomethan-d_3-amine



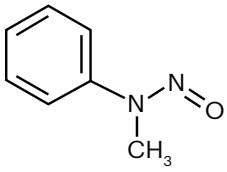
Molecular Formula: $C_2D_6N_2O$
CAS No: 17829-05-9
Uses: Internal standard for quantitative testing

N-Nitrosomethylphenylamine (NMPA)

Catalog #: 1466607

Category: USP impurity RS

Chemical Name: *N*-Methyl-*N*-nitrosophenylamine



Molecular Formula: $C_7H_8N_2O$
CAS No: 614-00-6
Uses: Impurity standard for quantitative analysis and other purposes by LC-MS and GC-MS

EXISTING NITROSAMINE IMPURITIES

Item #	Description	Item #	Description
1466641	N-Nitrosodibutylamine (NDBA) (1 mg/mL in methanol)	1466674	N-Nitrosodimethylamine (NDMA) (1 mg/mL in methanol)
1466652	N-Nitrosodiethylamine (NDEA) (1 mg/mL in methanol)	1466685	N-Nitrosoethylisopropylamine (NEIPA) (1 mg/mL in methanol)
1466663	N-Nitrosodiisopropylamine (NDIPA) (1 mg/mL in methanol)	1466696	N-Nitrosomethylaminobutyric Acid (NMBA) (1 mg/mL in acetonitrile)

View the Full Portfolio of Our Eight Nitrosamine Reference Standards at go.usp.org/nitrosamines-impurities

development of medicines that are safe and effective for everyone.

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Continuous: Before you Leap, Consider this

There's a lot of talk about the cost benefits of implementing continuous biomanufacturing, but where is the data?

By Niklas Jungnelius, Process Modeling Leader at Cytiva

The arguments in favor of moving to a fully continuous bioprocess are clear: a perfusion bioreactor is typically more productive than one operating in batch mode, resin costs in clinical production may be significantly reduced by switching to a continuous capture step optimized for productivity, and fully continuous manufacturing can essentially eliminate idle and hold times. Understandably, these examples get the spotlight – but I think batch production is unfairly overlooked.

We actually see little data to demonstrate significant cost benefits from continuous biomanufacturing on the whole. In fact, much of the process economic modeling data published suggests that batch production many times may be more cost-efficient. In my experience, productivity benefits identified for individual process steps rarely convert to cost savings of the same magnitude overall. Productivity benefits for the perfusion reactor are offset by the higher media consumption. Resin consumption benefits from continuous capture are, in commercial manufacturing, reduced to the advantage of overloading. Savings from a reduction in process size may be offset by the need for more sophisticated instrumentation, which in combination with longer run times, may increase risk of failures – this should also be factored into the total cost equation.

But what about full usage of equipment in continuous mode? Wouldn't this tip the scale to increased cost benefits? In reality, even though equipment may be used close to full time in continuous manufacturing, it may not be used to its full capacity because the productivity for every process step is determined by the bioreactor output. Therefore, the process steps following the reactor must be dimensioned to cope with maximal reactor output, plus a safety margin to handle variability. But they are often limited to run at the productivity dictated by the current reactor output. In contrast, idle times and scheduling in disconnected processing reduce equipment time usage, but allow for full productivity during operation.

All in all, given the built-in complexities and interdependencies in biologics production, we can't so easily declare continuous the winner when it comes to cost.

To complicate things further, in addition to production costs, a number of other factors may substantially impact the business case when choosing a production mode. In process development, for example, a continuous setup could provide benefits in terms of reduced scale-up efforts. By choosing a scale-out strategy rather than scale-up, it may be possible to run the same process scale from early clinical production to commercial manufacturing, saving development costs. But, with this strategy, is there a risk of reducing the benefits of scale in the production setting? And given the more challenging process development effort typically required for setting up a continuous process, how do you know when to implement continuous production for a molecule? What is the strategy? Should you invest in early clinical development, despite the high probability that the molecule will not make it to market – or should you hold off until late-stage development, risking a delay in time-to-market and associated loss of revenue? Additional considerations include impact on buffer management and the potential for production transfer options to be impacted by choice of production mode, making it more difficult or expensive to source capacity. All of these questions must be addressed prior to a strategic decision around preferred production mode.

Among my responsibilities at Cytiva, and one of the most enjoyable parts of my job, is working with customers to create data that provide a clearer picture of the pros and cons for continuous manufacturing. In cases where continuous manufacturing has clear benefits to product quality or yield, such as for labile molecules or when there is a very large difference in productivity between the perfusion and batch cell lines, it is easy to see the cost benefits of continuous manufacturing. For other molecules, it may be far from a given – we cannot assume that either production mode will be a home run for every application. In my view, we should keep an open mind to the solutions that best meet our individual needs and objectives.

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NEW TECHNOLOGY GIVES MANUFACTURERS GREATER VISIBILITY INTO FILL AND FINISH PROCESSES THAN EVER BEFORE

Technology is advancing rapidly and with it comes the potential to improve pharmaceutical manufacturing. At the end of 2020, Schott scooped the top place in our annual Innovation Awards for its Smart Container Technology – individually coded vials that give manufacturers the ability to track vials moving through fill and finish lines. Not only could this improve reject management and line clearance, but the data gathered could also influence process improvements. Regulations don't currently mandate that manufacturers implement this level of traceability in manufacturing, but companies are already looking to the future and evaluating how solutions like this can benefit their business.

We speak with Diana Löber, Global Product Manager Bulk Vials, at Schott, to find out more about the technology.

WHAT INSPIRED THE COMPANY'S INTEREST IN INDUSTRY 4.0?

We are increasingly living in a digital world and Industry 4.0 represents the next logical evolution of production. We are seeing greater use of automation and technologies are developing rapidly to enable faster, more efficient measuring and monitoring of production processes, allowing manufacturers to evaluate and optimize best practices. This guarantees that production has the best possible outcome.

There is also the future vision of implementing Industry 4.0 for real-time release testing of pharmaceutical products based on process data. A goal for the future could also be immediate direct release of the product based on high-quality process data. Real-time release testing opens up the opportunity to move away from batch production and toward continuous manufacturing. Production would flow with materials in continuous motion, eliminating batch-to-batch changeover and the constant interruptions batch production involves – but moving to continuous processing means that you need full traceability of individual products throughout the line. Our Smart Container completes another piece of the Industry 4.0 puzzle by providing this traceability of individual containers as they move through the line.

All of this, of course, will ultimately benefit human health by promoting the efficient manufacture of high-quality pharmaceutical products.

WHAT IS SMART CONTAINER AND WHAT ARE THE BENEFITS?

We add a small, unique identifier to every vial. This is done using a laser directly after the vial is produced, enabling traceability of each individual vial throughout the entire production chain. At the end of the fill-and-finish process, when the filled container is labelled and introduced to its secondary packaging, the unique identifier on the container can be matched with the mandatory code on the secondary packaging. This allows full traceability, which could save time and costs in the event of a product recall.

Traceability in supply chains is a frequent topic of industry discussions – but traceability during manufacturing, such as fill and finish, also has benefits. In my experience, customers are always concerned about the risk of mixups, which can have serious consequences for patients – and for a company's bottom line and reputation. Mixups often happen when a company fills in one location and packages in another, but problems can occur even when everything is performed in one place. Whenever there is a product changeover on a line, there is a risk that a vial from product A may be overlooked and then mixed in with product B. Line clearance is a very manual process and a real pain point for customers. If 1,000 vials went into the line, you need to be certain that 1,000 came out. And if you've ever observed or had to conduct line clearance, you'll know how tedious this is! Traceability of every vial would automatically tell you how many vials were unaccounted for without the need to count by hand.

Fill and finish is a complex process with many different points where issues can arise: washing, filling, capping, and more. If you could track and trace every container step by step, you would be able to identify where issues occur in the production line – and correct them. Often, when a vial is rejected, you will not know why without inspecting it, but traceability would tell you how the vial has moved through the line. If problems occur frequently in the same part of the line, that's a signal that something may need checking.

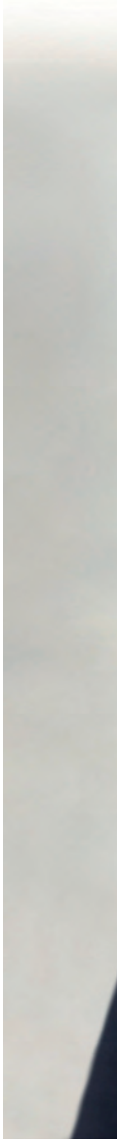
HOW CAN THE TECHNOLOGY HELP WITH LYOPHILIZATION?

Lyophilization is a highly complex process. It's not uncommon for products to develop defects or lyophilize incorrectly, but it can be challenging to pin down in exactly what part of the lyophilizer the problems are occurring. When developing a lyophilization process, manufacturers often apply sensors to certain vials that measure product temperature on different shelves so that they can see how the process is working and if there are problems. However, it hasn't been possible to track every single vial or where they are positioned inside the lyophilizer.

With technology like Smart Container, there is a code on every vial that can be combined with software to see which vial was standing exactly where inside the lyophilizer. This provides much deeper insight into the process. You will know that vial X in position X has a defect and that the vials around it also have the same defect. From there, it may be possible to adjust process parameters such as pressure and temperature.

HOW IS THE CODE ADDED TO THE CONTAINER?

Customers are always worried about changes that might impact container strength and, consequently, lead to an increased risk of breakage. Therefore, it was important for us to choose the right technique for adding the code. We use a very gentle laser melting process to apply a data matrix code to the container – and we have data to prove that the container maintains its strength after the code is applied. The process is very accurate – it is even possible to apply a code to the syringe



flange. The laser-marked code remains stable during the whole fill and finish process – through washing, autoclaving, and depyrogenation up to a temperature of 600°C.

With the laser marking technology, the data matrix code can be as small as one square millimeter (corresponding 14 x 14 dots). It can be either numeric or alphanumeric, containing 16 or 24 digits, which means several sextillion different possible numbers.

We approached the challenge openly by evaluating a number of different options. We excluded RFID early on because of costs and concerns around data security. RFID could also only be added later in the process, because it's impossible to edit it into the glass. We investigated ink, but that would mean bringing a new material into the production area. Most inks also wouldn't be able to withstand processing steps and the code could be scratched off, introducing the risk of particles and contamination. We experimented with ink codes, but the size of the code, as well as possible interference with inspection processes, meant that the results couldn't compare with those that we obtained from laser-marking the containers.

"All of this, of course, will ultimately benefit human health by promoting the efficient manufacture of high-quality pharmaceutical products."

HOW DID YOU DECIDE ON THE BEST LOCATION FOR THE CODE?

This was indeed a challenge! Right now, there are no regulatory rules to say where the code needs to be. We spent a lot of time talking with our customers to find the best spot for the code and ultimately placed it on the bottom of the vial. This way, the label does not interfere with the code. In addition, if the code were placed on the side, multiple cameras would be necessary to read it, or you would need to turn the vial, which isn't something companies want to do. Only a minimal change of line equipment is necessary to implement our solution. We also made sure the code was visible even when the vials are integrated into adaptiQ nests, our sterile ready-to-use solution.

HOW HAVE CUSTOMERS REACTED TO THE SMART CONTAINER SO FAR?

There has been a lot of positive feedback so far, with customers appreciating its forward-thinking approach. Customers have been interested in learning about the laser-marking technology and how we decided on this approach.

This level of traceability in manufacturing lines is not mandated from a regulatory point of view, but many pharma companies – particularly the big players in the field – are examining the area closely through roadmaps and are keen on making progress. It was reassuring for us to hear that there were teams working on this! Companies want to get ahead of the regulatory curve. The industry has a lot of experience with track and trace on secondary packaging, but now companies are keen to see how traceability can directly benefit manufacturing through increased visibility.

WHAT ARE THE NEXT STEPS?

Vials are the first step, but we also intend to expand to syringes. This is another reason we needed an accurate technology like laser marking. Syringes often arrive pre-sterilized in a nest. The best place for the data matrix code is the flange, because it can be easily read whether or not the syringes are in the nest. If the code were placed on the side of the syringe, it wouldn't be visible when the syringe was inside the nest.

In the future, it might also be possible to deliver manufacturing data about the unique vial (such as place and time of manufacturing or dimensional data) via the code. This is a vision, but it needs to be feasible from a production point of view and the data will need to be transferred safely to customers.

IS THE ADOPTION OF MORE INDUSTRY 4.0 SOLUTIONS INEVITABLE FOR PHARMA?

I believe it is an inevitable next step. Other industries have already moved in this direction, but pharma is often a bit slower because it is subject to heavy regulations. As a supplier to the industry, we have to support our customers and develop solutions to help them face the future. Industry 4.0 is certainly the way forward! I am delighted to have been involved with this project. This type of technology can help manufacturers improve their processes, which ultimately contributes to better patient safety – always the greater goal in this industry.

BOOSTING CELL LINE EXPRESSION

RUNNER UP FOR 2020: GPEX BOOST TECHNOLOGY FROM CATALENT BIOLOGICS

Featuring Gregory Bleck, Vice President of R&D, Catalent Biologics, and inventor of the original GPEx and leader of the GPEx Boost technology development team

WHAT ARE THE CONSEQUENCES OF POOR CELL LINE DEVELOPMENT?

Poor cell line development can result in cells that exhibit low expression or inconsistent product from batch to batch. Low expression means that more runs per year may be necessary or that runs may need to be performed at a higher volume – in either case, manufacturers are faced with higher costs. Moreover, inconsistent batch quality could result in a higher number of out of specification batches, which may need to be discarded; here again, cost is a major implication.

WHY IS INNOVATION IN CELL LINE DEVELOPMENT TECHNOLOGY NECESSARY?

There is a constant desire to increase efficiency and speed, and to reduce drug development costs. The cost of goods sold (COGS) can be high for biologics – they are complex after all. But this same complexity can also cause inconsistency during manufacture. One way to reduce COGS is to increase productivity of the cell line expressing the protein. In simple terms, cell line development allows us to expand the upper limits of biologics production.

HOW DOES GPEX BOOST WORK?

GPEx Boost leverages GPEx platform improvements and a glutamine-synthetase knock-out CHO cell line, enabling high titers and increased specific productivities. GPEx Boost uses the same technology – and benefits from the same proven stability – as our original GPEx technology, but it has enhanced benefits. To name a few: up to 10 g/l titer for standard mAbs, up to four times higher titers in difficult-to-express proteins, reduced ammonia build-up, and improved cell growth and viability. Also, GPEx Boost requires fewer process steps, which can result in three-week time savings – and there's potential to compress timelines even further.

The benefits of GPEx Boost have been demonstrated from low- to high-expressing proteins. For example, a low-expressing Fc fusion protein had seven times higher titer in GPEx Boost pools compared with traditional GPEx pools, and almost three times higher clonal expression; ultimately, we saw 7.4 g/l expression in the bioreactor. The same "boost" is also observed in mAbs as well; we've had a low-expressing mAb exhibit three times higher titer and a medium-to-high-expressing mAb exhibiting 1.5 times higher titer in GPEx Boost pools compared with traditional GPEx pools.

WHAT WERE THE BIGGEST CHALLENGES FACED WHEN DEVELOPING THIS TECHNOLOGY?

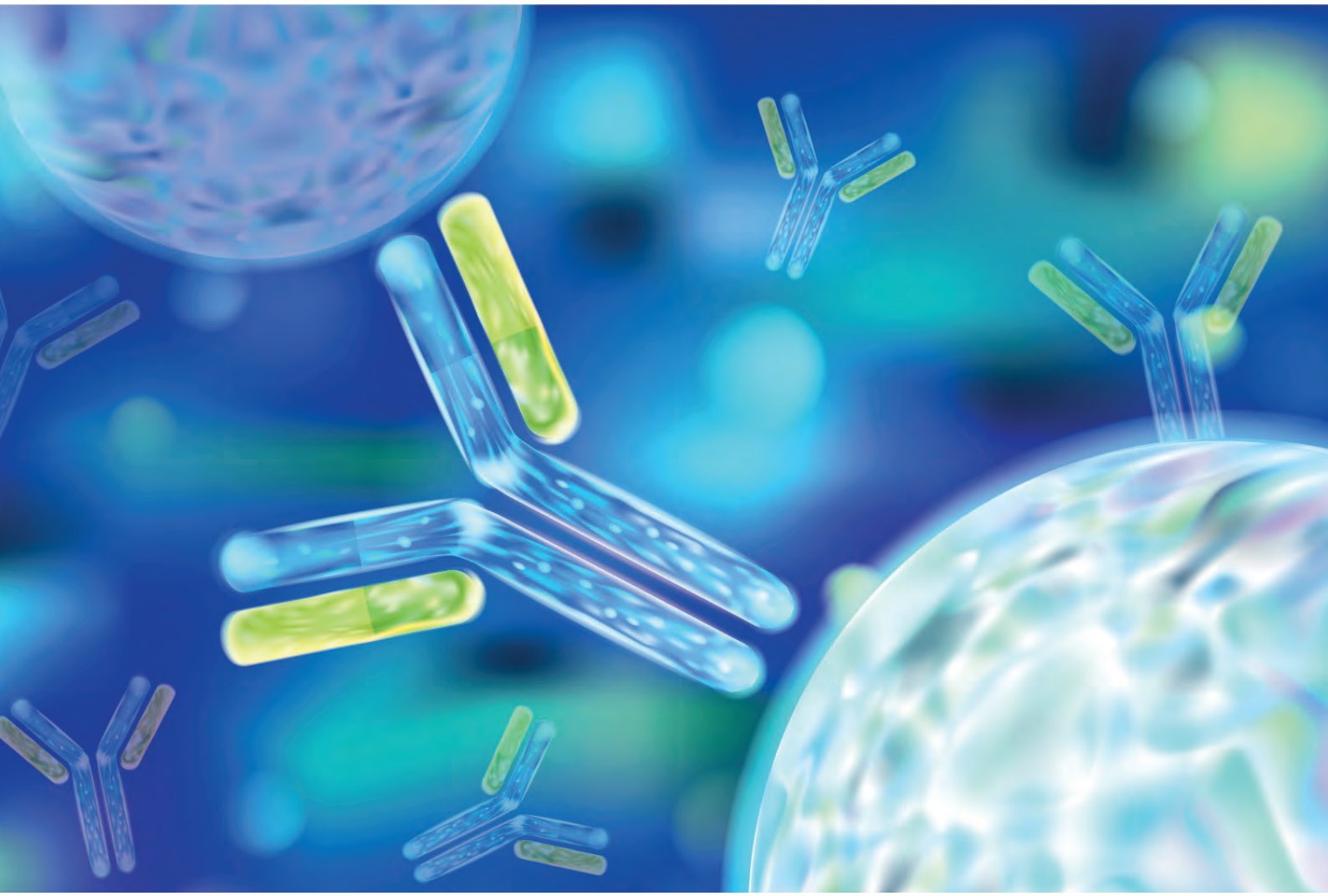
As cell line development is the first step in scaling up a molecule to clinical (and hopefully commercial) scale production, it needs to fit within a robust platform that includes clonal selection, process development, and scale up. As we optimized GPEx Boost technology, we looked to harmonize the culture conditions with the Berkeley Lights Beacon and Sartorius ambr 15 platforms to further streamline development timelines and costs.

HOW HAVE CUSTOMERS REACTED SINCE THE TECHNOLOGY WAS LAUNCHED?

The technology is used in over twenty customer programs, with many more programs under discussion.

WHAT OTHER IMPROVEMENTS/ DEVELOPMENTS WOULD YOU LIKE TO SEE IN OTHER CELL LINE DEVELOPMENT TECHNOLOGIES?

Ideally, cell line development technology would enable development of highly stable cell lines that would take the need for stability testing off the critical path. Additionally, cell line development technology should be robust enough to work with multiple different cell types and enable high expression of even complex molecules. Finally, cell line development technology should not require multiple selectable markers (antibiotic selectable markers, in particular, should be avoided) because



they put a strain on the cell culture and can limit the ability to generate cell lines that can express complex molecules, such as bispecifics.

AND WHAT ABOUT THE FUTURE OF GPEX BOOST?

Because GPEx Boost technology leverages the proven stability and titer of GPEx with the GS-knockout cell line, it provides the ability to generate stable, high-expressing pools. This also opens the door for future advancements of the technology that will provide flexibility in the cell line development and clonal selection approach. This flexibility will enable faster timelines to generating phase I material. As we know, speed to first-in-human studies is critical for many companies. Thanks to the synergies of the GPEx platform and GS-knockout, there is additional future potential to help companies get their therapeutic candidates into the clinic and to patients even faster.

GPEx Boost builds on the company's proven GPEx technology with enhanced benefits. The increased efficiency could lead to the use of smaller bioreactors (providing a greater number of facility fit options) or a reduction in the number of manufacturing batches necessary (potentially increasing production scheduling).

The cost of goods sold can be high for biologics, but improved titers can help reduce costs during development and commercial stages. Catalent Biologics claims that, based on expression data, GPEx Boost can significantly reduce the development batch costs for mAbs and recombinant proteins.

SUPPORTING PATIENTS DURING TREATMENT

RUNNER UP FOR 2020: ADHEREIT 360 BASE AND ADHEREIT CLIP FROM NOBLE AND APTAR PHARMA

Featuring Adam Shain, Director Business Development, Digital Healthcare, and Josh Hopkins, Program Manager, AdhereIT

HOW DID THE COLLABORATION BETWEEN APTAR PHARMA AND NOBLE GET STARTED?

Aptar and Noble had been working on digital health adherence and compliance solutions. Aptar was focusing on all types of delivery routes like pulmonary, nasal, dermal, and ophthalmic, while Noble was focusing on autoinjector programs. In 2019, Noble became part of the Aptar family of companies, and synergies were immediately identified. Since then, we have been able to leverage skill sets from both organizations.

WHAT TRENDS AND PROBLEMS IN HEALTHCARE INSPIRED THE IDEA FOR ADHEREIT?

Noble invested a significant amount of time in meeting with patients and quickly realized that there was an opportunity to improve adherence and decrease user errors in the biologic self-injection space. This stems from the fact that patients are expected to perform self-injections using autoinjectors outside of a healthcare setting, without any formal training or guidance. Furthermore, Noble learned that patients are incredibly anxious each time they handle the injection on their own. We wanted to provide a solution that could, in real time, guide patients through the self-injection process, provide them feedback that they are doing it correctly and track their injection history over time, which can ultimately help improve adherence to the biologic, so they receive the full benefit from it and lessen the likelihood of injection errors.

HOW DOES ADHEREIT WORK?

AdhereIT is a device that is used with an autoinjector to assist a patient in the self-injection process. It is designed to work with a wide array of autoinjectors currently on the market thanks to modular inserts. It works by using various sensors to detect the outputs from the autoinjector during the injection process, and through audio and visual feedback it will alert the patient if they are using the autoinjector correctly or incorrectly, such as removing the autoinjector from their injection site before completing the injection. In addition, the AdhereIT device transmits patient performance results via Bluetooth technology to an app that allows the patient to track their injection performance.

WHY IS IT IMPORTANT FOR PHARMA MANUFACTURERS TO DO MORE TO ENCOURAGE PATIENT COMPLIANCE?

We all know that one of the biggest challenges the healthcare industry faces is patient adherence to medication regimens. Drug therapies cannot work if patients do not take them and treatment success is critical to the health of many patients. There is very little visibility of what occurs to a drug once it leaves the pharmacy. A successful refill does not ensure compliance to treatment, so having better ways to close that feedback loop of really understanding how patients take their drugs is a critical missing piece in the patients' longitudinal treatment journey. It is a known fact that one of the biggest hurdles to any chronic disease is patient compliance. So,

AdhereIT can integrate with self-injection devices to support patients with initial onboarding and ongoing adherence to therapeutic treatments. The base and clip provide visual, audio, and haptic feedback during the injection process to guide dosing success. Encrypted data is then transferred to a smartphone app, which also incorporates patient resources, such as training videos, injection reminders, and drug reorder notifications.

Data can be shared with healthcare providers to track patient performance through a dashboard, providing real-world data to support ongoing therapeutic programs. Aggregated, anonymized data can also be made available to pharmaceutical companies to help address poor adherence.

it is critical for patient health that we make the ability to take their drug as simple and fearless as possible. With AdhereIT, pharma manufacturers are better enabled to encourage patient adherence and help them achieve better health outcomes.

HOW HAS THE PANDEMIC AFFECTED ATTITUDES TO AND UPTAKE OF DIGITAL TECHNOLOGY IN HEALTHCARE?

The pandemic has acted as a rapid accelerator for digital health products and programs as patients have less physical access to healthcare providers. Because of this, the patient population was forced to find new ways to engage for ongoing treatment. Prior to the pandemic, there was a heavy resistance to go digital, but now we see new trends arising in telehealth where some insurers may even encourage telehealth visits prior to an in-office visit for some conditions.

COVID-19 has also had a great impact beyond patient-facing healthcare; pharma companies across the globe have been forced to rethink the most effective ways to conduct clinical in-person clinical trials with patients. In our view, digital technology, including connected devices like AdhereIT, is revolutionizing the industry for both patients and pharma companies alike.

WHY DO YOU THINK CONNECTED MEDICAL DEVICES ARE THE FUTURE OF HEALTHCARE?

Understanding the patient journey is a critical tool in developing successful treatments – and understanding how medications are utilized in the real world is an important missing piece in the ecosystem of digital health. By creating new ways to both understand and engage with patients, we will not only make better therapies, but we create more compliant, confident, and healthier patients.

NOMINATIONS FOR 2021

The Medicine Maker Innovation Awards highlight the top technologies released over the course of the year. Nominations are now open for the 2021 Innovation Awards. To nominate, fill in the simple form available at: tmm.txp.to/innovation2021

What happens next? Nominations will be assessed by a judging panel and the top technologies of 2021 will be showcased in the December issue of The Medicine Maker. The final winner will be decided by a public vote in early 2022 and will have the opportunity to discuss their innovation in more detail in a future issue of The Medicine Maker.

The rules? The technology must have been released (or planned for release) in 2021 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 Thursday 28 October.

Questions? Contact the Editor: stephanie.sutton@texerepublishing.com. Due to the volume of entries we expect to receive, we will only contact those chosen to be highlighted in the December issue.

View the 2020 Innovation Awards showcase here: https://themedicinemaker.com/manufacture/the-innovation-awards-2020

Best Practice

Technology
Quality
Compliance

Clinical Trials – and Tribulations

Why isn't pharma embracing digital technologies to not only improve but also boost diversity in clinical trials?

By Maryam Mahdi

Clinical trials underpin the infamously slow drug development process – and they are almost guaranteed to add to timeline woes. But is the industry taking full advantage of the software and technologies at its disposal? The events of the last 12 months have proven the power of (remote) technology – and the first approved COVID-19 vaccines prove that there is room for rapid development.

Here, Parag Vaish, Chief Product Officer at decentralized trials platform Medable tells us about the obstacles facing those who wish to adopt decentralized trial platform technologies, how they can improve studies, and how pharma can be more inclusive in and beyond the clinical trial landscape.

How did your interest in clinical trials begin?

In 2015, I met Jonathan Bush, co-founder and CEO of Athenahealth – a provider of cloud-based services for healthcare apps. At the time, medical mistakes were the third-largest cause of death in the US and the lion's share of those were related to adverse drug interactions. These statistics prompted Bush's wish to expand the company's mobile encyclopedia for drugs – Epocrates – to include search tools for diagnostics and procedures. He envisioned the platform connecting with electronic health records, automatically scanning patient data to spot drug conflicts, head off critical errors, and potentially save thousands of lives. It hooked me because it showed that the problems healthcare and pharma companies faced were resolvable.

It's amazing what software can do for humankind and I wholeheartedly subscribe to the idea that it can enhance clinical trials – streamlining the consent process, making trials more accessible, improving efficiency, and reducing costs. If we can achieve these goals, we can improve (or even save) lives, decrease patient expenses, and bring new medicines to patients faster. It may not be easy, but it is incredibly valuable work.

What aspects of clinical trials need the most attention?

Two areas particularly interest me: trial accessibility and the reduction of process friction. It takes a decade to bring new drugs to market using conventional, highly manual approaches. These timelines could be shortened (and issues ironed out) using available and emerging technologies. A decentralized model, for example, could theoretically improve accessibility by allowing greater participation from a broader patient demographic. You would only need to provide patients with an app that they could access both at home and onsite.

Such tools can also enhance the patient consent process. Currently, trial participants are asked to fill in forms as long as 60 pages. Digitizing these forms could make them easier to follow, harder to lose, and even permit translation into patients' preferred languages. Of course, it's critically important that participants truly engage with the documents and understand the trial, but digitizing the forms can also improve patient retention – a significant challenge in clinical research today.

Many of these technologies are well within the industry's reach. Did you know that most smartphones have user settings for sensory conditions that affect phone use? If similar technologies can improve the patient experience, then what's stopping us from transforming the trial process?

Why do clinical trials lack diversity?

A central challenge is that traditional site-based studies tend to be located in areas that are not wholly representative of the broader population. On the other hand, expanding the patient pool beyond the site area can place a significant travel burden on patients and even prevent some from participating. In 2018, a study evaluating the data of 1,600 cancer

clinical trial participants showed that patients traveled an average of 41.2 miles for phase I studies! For some patients, the cost of travel, time off work, or lack of childcare make trial participation an unrealistic goal. A decentralized model largely alleviates these burdens and can lead to greater trial diversity.

But beyond the geographic issue, there is an advertising problem. Most people learn of a new study through their doctors, but sometimes not even clinicians are aware of the latest clinical trials. Proactive patients may find them through extensive research, but this requires a great deal of effort (and possibly medical knowledge). And, unfortunately, trust remains a major factor in recruitment. People from some ethnic backgrounds have a longstanding distrust of the healthcare system and the doctors directing them to clinical trials. (A Kaiser Family Foundation poll found that only 60 percent of black adults in the US said they trust doctors to do what is right most of the time, compared with 80 percent of white Americans.)

What's the best approach to tackling diversity challenges?

I learned a great deal from my time in the automotive and commerce industries. When I first joined Tesla, it was a very intense environment where diversity was not prioritized. From my first month at the company, the inequity was obvious: my team of eight included just two female employees, who were also the lowest paid by at least 20–30 percent. As the team grew, I made a conscious effort to correct this by hiring more women and eliminating the gender pay gap. In my view, building lasting trust relies on equal treatment. By organically eliminating inequities rather than imposing strict corporate policies that may have been viewed negatively, we prompted a cultural shift. As more of the existing team received equal and fair pay, my candidate pool effortlessly included more women.

At Athenahealth, I learned a lot about unconscious bias. Meetings of 20 people – five of them women – would often start, "Hey guys, we need to solve X problem." Unintentionally, we were implying that women were not fit to address the issue – so I started to change my language to help create a more inclusive environment.

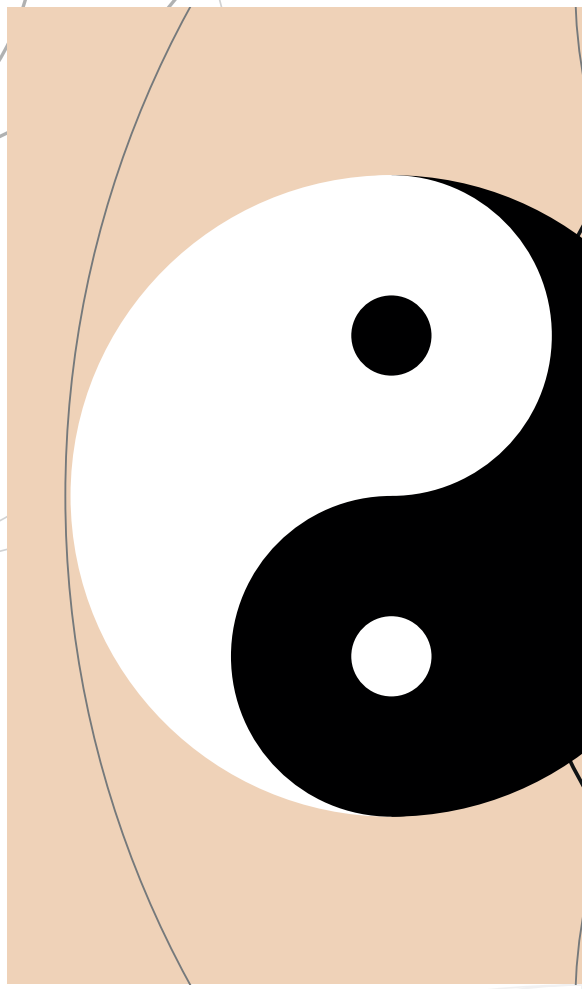
Both experiences taught me that anyone can make diversity a priority. You do not need institutionalized policies. Respected leaders can create a work environment that innately attracts diverse talent simply by modeling the right behavior. And we can apply the same idea to clinical trials. If we consider the needs and requirements of a broad spectrum of patients, we can improve the way we conduct trials – and improve participation across all patient groups.

How can the right behavior be modeled?

We must drive awareness on an individual basis. Policies are often difficult and slow to implement – but, by increasing individual awareness of diversity issues, we can make progress faster. I would advise companies to educate their leaders and then empower them to create tight-knit team environments that continuously (and naturally) increase awareness and diversity. As leaders, we need to be the change we wish to see. Only then can our colleagues follow suit, not because of a corporate policy, but because they respect the leaders who teach by example.

The Human Yin to the Clinical Yang

Humanizing clinical trials through patient advocacy



Even though digital platforms are making a difference, could the patients who engage with them be given a stronger voice?

Gaurav Dave and Allison Kalloo are on Medable's Patient Advisory Council (PAC) – a patient group that advises Medable and its biopharma customers on how to improve patient access, experience, and outcomes in clinical trials. Here, they outline the barriers to engagement with the trials process and share their views on how the industry can improve its relationship with its most important stakeholders.

How do advocacy groups benefit patients?

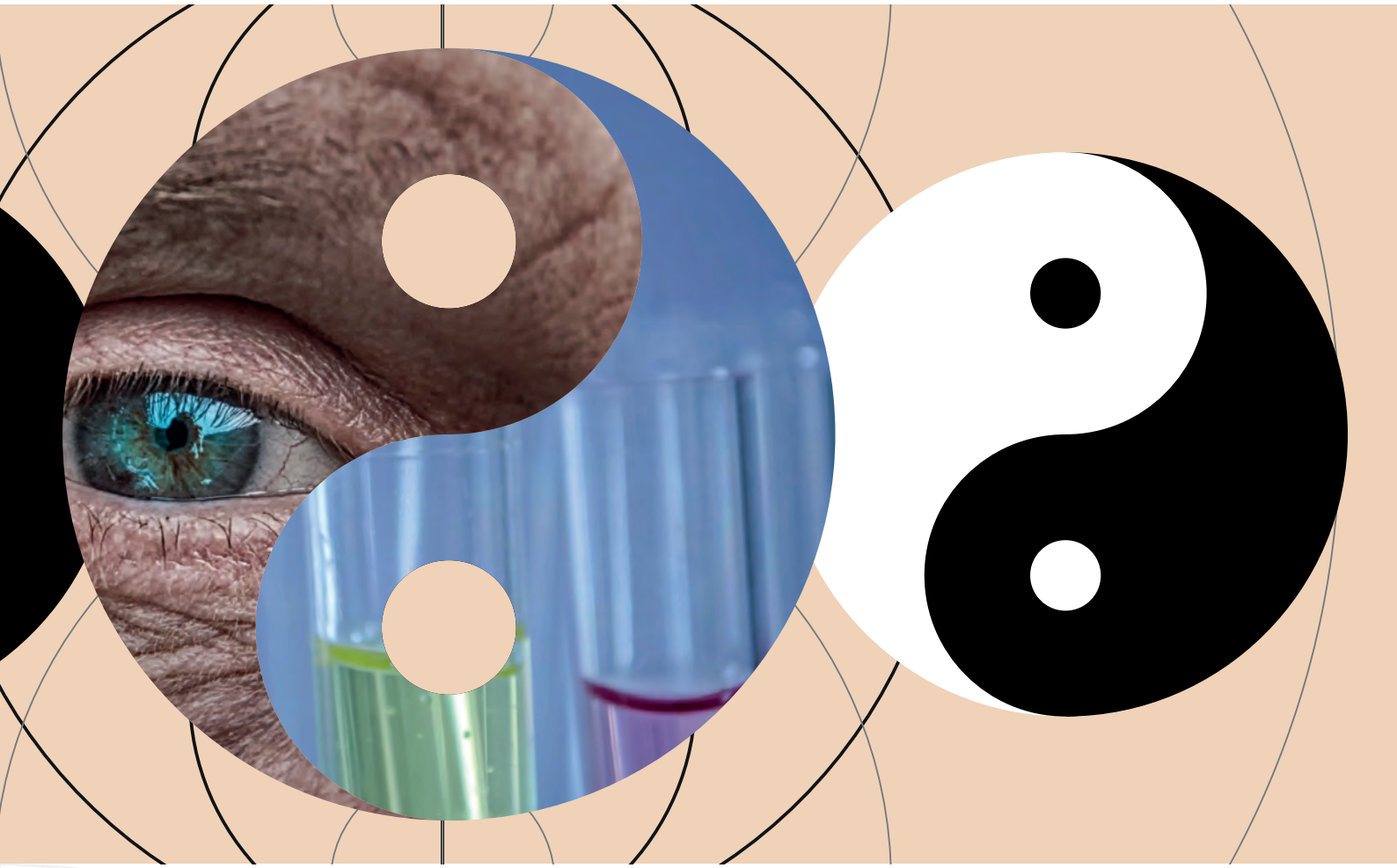
Kalloo: Institutional review boards and ethics boards have their place, of course, but advocacy groups make patients feel seen and heard. Patient advocacy is the human yin to the clinical yang. Patient advocacy groups are the soul of the larger clinical trial body that amplifies patient voice and provide meaningful feedback to identify and reduce participation barriers.

Dave: Patient advocates foster the mission of improving lives. It is easy for the industry, the healthcare system, and the clinical providers to consume themselves in the intricacies of delivering healthcare or conducting research. Amidst that dynamic, intense, and complex landscape, patients' voices can go unheard. Unbiased patient advocacy groups can be a critical element of the system that connects patients with the clinical research community.

Patient advocacy groups build working partnerships with the healthcare and pharmaceutical industries and change clinical research narratives. For instance, they can serve as trusted allies to ensure transparency of the clinical trial processes. Further, they can help address today's digital divide and break down barriers to access among disparate and historically marginalized groups. Similarly, they can advocate for and foster the recruitment of a diverse group of trial participants, specifically in underrepresented and underserved populations – especially now as companies are essentially removing many of the common barriers for participation with decentralized clinical trial platforms.

Historically, have partnerships between pharma companies and patient advocacy groups been successful?

Dave: Certainly, there have been successful partnerships between pharmaceutical companies and patient advocacy groups. However, this success is dependent on transparency, ethics, and accountability. The USA's National Health Council, which comprises various patient advocacy groups, business organizations, and pharmaceutical companies, has operationalized 38 standards of excellence. These standards range from requiring diversity to rules around fundraising to whistleblower policies to reporting. Each member organization abides by these standards



"Patients and their advocates have been consistently made to feel as if big pharma was simply going through the motions."

of excellence to ensure prioritization of patient safety and foster health equity.

However, success between the life sciences industry and civic groups is highly dependent on trust, accountability, and commitment to meaningful stakeholder engagement.

Kalloo: I have witnessed multiple successful collaborations up close, but any substantial outcomes that were meant to benefit patients have often been wrought with frustration, effectively stemming from a power struggle and tone-deafness on the part of the industry. Patients and their advocates have been consistently made to feel as if big pharma was simply going through the motions, with no intention of following through with their recommendations. In the end, patient voices were frequently disregarded. But some companies are working to change this by deploying patients' recommendations into patient-centric technology solutions. This shows up in patient diaries that ask more precise questions and leave less room for personal interpretation, in study tools that require less maintenance, and in wearable devices that are sleeker and less clunky.

What barriers prevent patients from participating in advocacy groups?

Kalloo: The most significant barriers are those of perception and the power balance. If people are going to spend precious time providing patient expertise, we want to know that it will be used. We deserve a return on our investment, too. Against the

Meet the PAC

Allison Kalloo is a patient recruitment specialist and the founder of Clinical Ambassador and iParticipate, Inc.

"Long before I thought to put a label on it, advocacy has been my modus operandi. But it would be unfulfilling if I were not working toward goals that benefit other people. As a longtime patient advocate and an ambassador for diversity, equity and inclusion in clinical trials, both in my Clinical Ambassador work and also as a member of the Medable PAC, I am inspired by opportunities to broaden my reach and pay it forward in tangible ways."

Allison Kalloo

Gaurav Dave is an Associate Professor of Medicine, Associate Director of the Center for Health Equity Research, and Director of Abacus Evaluation Consulting at the University of North Carolina at Chapel Hill.

"Patient voices are continually lost in the ever-growing maze of the healthcare system. Not knowing what questions to ask, not understanding the medical or research jargon, not having the resources, and not participating in joint decision-making perpetuate this problem. These issues are structural and systemic. Since the historical exploitation of subjects in research – (e.g., Tuskegee study) – these concerns continue to instill distrust, reducing the odds of achieving equitable patient-centered treatment."

backdrop of industry's enormous profits, the intel collected from patients should be treated with the same reward calculus. Patients are invaluable research partners, whether in formal advocacy roles or not, and should definitely be better compensated for their time and contributions across the board. Likewise, advocacy groups should not have to struggle for donations to support their programs. They shouldn't even have to ask. Mere accolades and annual awards banquets are not enough. We are all doing meaningful work in this space, albeit in different ways. Not feeling respected by research entities can prevent patients from participating more fully and can make advocacy groups leery about providing referrals.

Dave: Take this as one example; how does a Type 2 Diabetes patient living in a rural setting, working two jobs, and suffering from food insecurity access reliable clinical research information and find time to advocate for their unmet health-related social needs? How can we create systemic change that addresses such issues? Researchers, clinicians, decision-makers, and the industry need to change the research paradigm to ensure stakeholder engagement and a human-centered approach to patient advocacy.

Like Allison says, patients are research partners, yet the current clinical landscape places the onus on them to advocate for themselves in a complex ecosystem. And that needs to change. We should think of patient advocacy as the norm and patient-centricity as foundational, with decision-making in the industry driven by contextualizing diversity, inclusion, and equity as the gold standard for its practice culture. Without these structural and systemic changes, patient advocacy will continue to lag, preventing people from actively adding their voice and value to clinical trials.

What is the best approach for improving trial accessibility?

Dave: We need to rethink trial design, protocols for the site, participant recruitment, marketing materials,

The Tuskegee Syphilis Trial

Between 1932 and 1972, the CDC and the US Public Health Service conducted a study – arguably one of the US' most controversial: the Tuskegee Study of Untreated Syphilis in the Negro Male. The organizations recruited African American men to participate in trials to observe the effects of syphilis in untreated patients. However, the participants were unaware of this. They were under the impression that the study, which was initially intended to last for six months, would give them access to free healthcare for conditions, including syphilis and anemia.

Though penicillin became a recognized treatment for syphilis in 1945, the trial participants were never offered the antibiotic and the study continued for a further 27 years. Concerns about the ethical soundness of the study grew following an exposé written by the Associated Press in 1972. Responding to the public's reaction, an ad hoc advisory panel was formed to review the ethical approach taken. The members of the committee concluded that the men involved had been misled. By 1973, a class action lawsuit was filed that resulted in an out-of-court settlement. In 1997, Bill Clinton issued a formal Presidential apology.

For more information: www.cdc.gov/tuskegee/timeline.htm

"Equal access to participate in a clinical trial does not mean equity for all groups."

dissemination plans, and feedback loops with coordinators. A significant barrier to trial success is the lack of competent study coordinators who know the clinical trial processes and protocols for implementation. Another obstacle is the trial team's inability to recruit and retain participants (in some cases up to 80 percent). These and other barriers exist because we fail to i) standardize clinical trial staff requirements, ii) invest in training them in the intricacies of clinical trial conduct, and iii) design inclusive, equitable recruitment plans.

Equal access to participate in a clinical trial does not mean equity for all groups. For example, if a clinical trial staff creates an online marketing plan for recruitment, technically, everyone has equal access to that information. But can someone in a rural setting with broadband issues and dwindling technology infrastructure access that information? It is vitally important to consider systems and infrastructure that the research team can leverage. The team should include and invest in a robust community stakeholder engagement plan as part of recruitment. I would further argue that such a plan should be mandatory for proposals and protocols for all investigator-initiated, federal-, and industry-sponsored studies.

Kalloo: Gaurav is right – understanding that social determinants factor into study participation is pivotal. But the best way to find out how to improve recruitment and retention is to ask patients who should be invited, including them as much as possible. As an extension of that premise, I advocate that mock trials be integral to all protocols developed to collect qualitative data as early as possible in the study lifecycle while there is still pliability. Patient centricity – if it is to be authentic – is not a KPI that can be measured from the outside. Improving trial accessibility can be nuanced, especially for patients of color and other marginalized groups. But patient-centricity starts by asking the right questions of the right patients who reflect the study demographic. Collect patient intel early, properly compensate patients and advocates who weigh in, and then invest in implementing their suggestions.

How can pharma get it right?

Dave: It's vital to take a patient-centric approach. The population, particularly communities of color, does not trust the pharmaceutical industry because of years of perceived exploitation by the healthcare industry. Therefore, it is incumbent on pharmaceutical companies to be intentional and invest in building and sustaining a relationship with the public. Be transparent and accountable. And please support patient advocacy groups with the resources that are critical to their operations, engagement, and sustainability.

Kalloo: Pharma can get it right by committing to equitable representation of people of color in every trial. By designing study protocols that are based in reality. By humanizing the clinical trial process — even in decentralized trials. And by holding space for people without advanced degrees and clinical backgrounds to contribute to how that looks and how to get it done.

People, Process, Product: Lessons Learned with Antoinette Gawin

Antoinette Gawin, President and CEO of Terumo Blood and Cell Technologies, explains how a random act of kindness set her on the path to becoming a VP in her 20s. Antoinette shares her lessons learned overcoming adversity to succeed in finance, utilities, M&A and – finally – cell and gene therapy.

A random act of kindness could change someone's life

I grew up in a town of about 400 people called Cedar in Northern Michigan, USA. It was an immigrant farming community and very few people went to university – especially girls. People would ask, "Why would you go to university? Don't you want to be a mom someday?" even though I was at the top of all my classes. I didn't know anyone who'd taken a different path. But to earn some extra cash, I used to clean houses for wealthy people. I remember serving one gentleman who was having a company retreat at his house. The guests found out I was doing well in school and asked what I wanted to do. I replied, "What do you do?" They tried to explain their business, but I just couldn't grasp what they actually made. On the farm, we grew cherries or potatoes. It's strange to think back to that naïve girl and where she ended up!

That conversation widened my horizons and influenced my decision to go to the University of Michigan on a scholarship – but it almost fell through. As part of the full scholarship I received, you needed a local bank account with at least US$200 in it. I couldn't imagine having $200 sitting there, so I just said, "Well, that's not going to work." Some people from the University visited and I explained that I couldn't go because of the money – and this gentleman, Dick Baker, opened his wallet and gave me $200 there and then. I sometimes think about that random act of kindness because it changed my life.

I studied economics and English and wanted to be a lawyer. But, after I finished undergrad, I couldn't imagine continuing in school. So I went to GE in part because they had a leadership program that allowed you to get a "GE MBA," which involved a lot of coursework as well as rotational assignments across the company. That provided the foundation for the rest of my career. The program was "sink or swim" and you were thrown in at the deep end – but, if you were a hard worker, you could achieve just about anything.

Anyone can get their head around complicated topics, as long as they are relatable

Some of my first roles within GE were leveraged buyouts. I didn't even know what an LBO was when I first joined this global conglomerate. Returning home, my family would ask me to explain what I did, and I just couldn't. You're talking about high finance and they're reading the news about people in the industry doing all sorts of unethical things. So I used to say, "I sell refrigerators."

It was a good lesson in communicating the science behind cell and gene therapy, because we can isolate ourselves with jargon, acronyms, and scientific terminology. When I was growing up, my rural community didn't have access to the information everyone has at their fingertips today. People didn't question their doctors or try to understand why they were being prescribed a medication. This is changing now – and I've come to realize that there are ways to make anything accessible to the average person.

For example, now I tell my family that we make the equipment that collects and separates blood, which anyone

can get their head around. Cell and gene therapy is a little trickier. Even so, most people have either donated blood or had a transfusion themselves, and many will know someone who has had a stem cell transplant. As long as there are corollaries to their experiences, people will be able to conceptualize most things.

Never underestimate the power of reading old books!

As I mentioned, I started in the financial services sector for GE. Then, I went to what was called GE Information Services. This was pre-Internet and we were selling some of the first versions of email – so I found myself running an IT business. At one point, I was running GE's global data centers. It might sound archaic, but I grew up in a time when people said things like, "A woman can't run a data center – it's too complicated." Often, I was the only female in the room. That can be depressing sometimes, but it also gives you the fire to prove to people that gender doesn't matter.

One thing I realized is that you need powerful language to be able to convince people – so I often relied on my skills as an English major. When reading old books (I specialized in medieval literature), you are tasked with looking at something people have been studying for hundreds of years and finding something new. Then, you need to convince people of your findings and their significance. This art of unpacking the written word is invaluable when you're trying to connect an IT engineer, an automotive manufacturer, and a salesperson, for example. You need to find common ground between people who basically speak different languages. The ability to read between the lines to abstract what's important, and to use words to align people around a common goal, has stood me in good stead while moving between some very complicated sectors.

Next, I transitioned into GE's utilities business, which involved working with governments across the world. I worked in Switzerland for a while, running an acquisition there in the utility space. Then I came back to the States – partly for family reasons and partly to transition into healthcare and life science. I strongly believed my economics background and my experience working with governments would serve me well in understanding how healthcare systems worked.

Put the right people in the right roles with the right resources and the product will follow

After spending more than two decades at GE, I joined Baxter in 2009 to oversee global

market access and commercial excellence, strategy, and commercial operations. Then, in 2016, I joined Terumo Blood and Cell Technologies, becoming CEO in 2019. The company was originally a startup from Lakewood, Colorado, that grew by being acquired by other companies that were interested in the technology. One challenge that comes with that is that the business as a whole wasn't fully integrated. My task was to connect the dots. I had to bring all the disparate groups within the company – from China to the US to Belgium – and align them around a single goal.

I started with the basics: put people into the right roles, provide them with the right processes and tools, and the product will come. I had to make sure we had clarity on what we were trying to achieve. What were our governing philosophies? It can sound like motherhood and apple pie but, if you don't have clarity on these broader things, it can be very difficult to make concrete business decisions.

The company had been working in the cell therapy space for the past 20 years – for example, with companies like Novartis. When I joined, the first CAR T cell therapy approvals were on the horizon. We realized the power of our work in that area, but we also felt we could be doing a lot more. So we started to bring more clinical and scientific people from the cell therapy space and realigned our focus toward cell therapy development. We'd learned a lot from our blood centers, but cell therapy is a wildly different market and we realized we couldn't copy and paste old models of working.

A few years later, we launched a product in the advanced therapy space and signed several partnerships, including one with Kite. There are companies now using our technology at the preclinical stage and as part of their processes going into regulatory filings for clinical development.

Moving into cell and gene therapy was another step into a new, exciting, and complicated field. But that's something I became used to during my time at GE and at Baxter. I always say, "I'm not smart enough to cure cancer, but I might be smart enough to connect the dots between the people who, together, might cure cancer."

Convince the nastiest person in the room

Thinking back to the challenges I've faced in my career, being a working mom throws up quite a few! You have to constantly think about efficiency and keeping the peace. So much of business is about relationships. How do you balance tensions? How do you spend the time required to go deep into an area without missing the overall picture?

I've spoken about often being the only female in the room. Earlier in my career, I was also often the youngest person in the room too, because I became a VP at 29. People would actually tell me their granddaughters were my age! But I always advise people not to be afraid to show vulnerability. If there's someone you feel comfortable speaking with, catch up with them after a bad meeting and tell them you felt dismissed. Ask them what they would advise you to do differently. And, sometimes, you have to go to the nastiest person in the room and try to build that bridge. Of course, it doesn't always work – but if the nastiest person becomes your advocate, the rest will probably follow.

On the subject of diversity, although some things have changed, there is a long, long way to go. For example, I'm on a medical device industry board and there are just four women and two people of color. And the industry has collected data that suggest we've actually fallen behind in some areas. Although there are examples everywhere of people succeeding, we still have so many stereotypes. I still feel that diversity is something we have to convince people of – that we need to make a business case for it.

My philosophy is based on respect: respect all voices, hear all voices, and you will have very different ideas. And, in the life sciences, you have to reflect the people you serve. We treat sickle cell disease, which is predominant in the African American community. How can I understand that patient experience if I don't have any African Americans on my staff?

Personally, I learned not to have a chip on my shoulder. You need a thick skin, but you can't forget your strengths. I'm an empathetic person. If we miss a number, I take it personally – even if I try not to! But being empathetic also makes you a strong leader – people want to follow you if you genuinely care about them.

My mother used to say, "I can't smell what you're thinking"

One of the most important lessons I've learned throughout my career is the importance of personal courage. When you have courage, people come to you because they see you as a catalyst for change. This is particularly important for women and for people from minority backgrounds – those who traditionally might not have had a seat at the table. Well, now you've been invited to dinner, so why not get the conversation going? I always think in terms of risk – what is the real risk of speaking up? So have that personal courage, because it creates momentum and energy that people will naturally follow. Be the catalyst and create the environment that you want to see. As my mother used to say, "I can't smell what you're thinking."

Another important lesson is getting the order right: people, process, product. Leaders really need to understand people – everyone has a backstory. If you understand what they're thinking about and what motivates them, you can put the right processes in place for them to achieve their goals. From there, the products will follow.

Finally, I always advise people to surround themselves with unconventional wisdom. It's easy to go down the hall and talk to a person you've known for a long time – but you run the risk of creating an echo chamber. Seek out people you don't see every day. Perhaps there's someone from a different department, from another country, who speaks a different first language. Talk to that person. You never know what you might learn!

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Understanding the Three Levels of Genetic Medicine

ASC Therapeutics is using a new type of stem cell derived from human placenta to treat graft-versus-host disease, as well as tackling hemophilia with gene and CRISPR therapies. To find out more, we speak with Chief Medical Officer Oscar Segurado, who also stresses the importance of helping patients understand the difference between gene therapy and different kinds of gene editing involving CRISPR.

How did you get into cell and gene therapy?

Following my medical degree, I went into research; specifically, molecular biology and immunology – there was no cell or gene therapy! I published several papers on tumor infiltrating lymphocytes: the T cells that recognize tumor cells. This work took place years before therapies such as checkpoint inhibitors led to the explosion of cancer immunotherapies, so we did struggle to find ways of preventing tumors from evading the immune response. But you might say we and other research teams were building the foundation for what would later become CAR T-cell therapy.

After spending some time working in diagnostics, I moved into biologics. We were engineering monoclonal antibodies – and, at that time, it was the coolest thing you could imagine! In particular, we were focused on anti-TNF therapies. I was the senior medical director for the team behind Humira – the first fully human monoclonal antibody approved by the FDA and currently the world's best-selling drug therapy. And that's where I really learned the complementary roles of clinical development and medical affairs. After working with several biotechs to speed up therapy development and diagnostics, I joined ASC Therapeutics as Chief Medical Officer. The company has two main development programs – one in gene therapy (including CRISPR-based gene editing) and one in cell therapy.

"We were engineering monoclonal antibodies – and, at that time, it was the coolest thing you could imagine!"

Can you give me an overview of your gene therapy development programs?

Our gene therapy program is in Hemophilia A, which is caused by a genetic mutation leading to a lack of the clotting factor VIII. We are introducing the missing gene, using a viral vector, to the liver, which allows the hepatocytes to begin producing the missing clotting factor. With a single infusion, we essentially restore the entire machinery that produces the factor. We also have a gene editing program in Hemophilia A, which is in an earlier stage, and can complement gene therapy with the ability to treat the pediatric population.

I should also mention that we are working on something that we believe will redefine gene therapy – at least in the liver. Consider what happens when you introduce your circular DNA into the nucleus of the cell. The process begins with transcription to produce the mRNA. Once the mRNA leaves the nucleus, you begin the translation into the protein, which takes place in the endoplasmic reticulum. We have found that the proteins produced by the circular DNA do not fold in the exact same manner as proteins transcribed and translated from the chromosome. Sometimes the cell will react against an incorrectly folded protein in the endoplasmic reticulum, which is called the unfolded protein response. This can trigger inflammatory responses against the producer cell and reduce the efficiency of gene transfer. In our clinical trials we will thoroughly assess what role the unfolded protein response plays in the success rate of a gene therapy, and hopefully find a solution to the problem.

Can you explain the main differences between gene therapy and gene editing? What are the advantages and disadvantages of both approaches?

With gene therapy, you're not inserting the DNA into the actual genome. You insert the viral vector into the nucleus – but outside of the chromosome – to produce the desired protein. In short, if the cell duplicates, you're not going to maintain that circular DNA and the new cell won't produce the desired protein. If we take our work in hemophilia A as an example, we know that hepatocytes in adults are very stable, so they should be able to keep producing the protein via the circular DNA we introduce for a long time. We don't know how long yet – it could be five years; it could be 30 years. But this means we can only treat adults, because younger people's hepatocytes will divide and lose the circular DNA we have inserted and the new cells won't produce the clotting factor VIII. Therefore, gene therapy is limited to stable cell populations.

With gene editing, you introduce the gene directly into the chromosome using a tool such as CRISPR/Cas9. And that means any dividing cell will retain the edit introduced by the enzymes and, in the case of hemophilia A, you could treat someone under the age of 18. The downside of this approach is the risk of introducing unwanted – and potentially unknown – changes into the genome. Developers must ensure their gene editing therapies do not introduce harmful off-target effects, which is why timelines can be considerably longer compared with other kinds of therapies.

Do you think cell and gene therapies are more complicated for patients to understand than small molecule or biological therapies? Are patients fully aware of how these therapies work and the potential risks involved?

I think most people have a very limited understanding of their genes, genomics, gene therapies and so on. I also doubt that the average patient would know the difference between a gene therapy and gene editing. But it's an extremely important distinction because people are often concerned about the ethics of manipulating genes. So we need to clearly explain these issues, and I like to do that in terms of three levels. First, you have gene therapy, which, as we've discussed, cannot be transferred to dividing cells. Some patients become concerned when you explain that we will be using a "viral" vector. So we must make sure they understand that this is an harmless or inactivated virus – it is not a pathogen.

Then on the second level you have targeted gene editing, which can be transferred to a dividing cell but cannot be inherited by the recipient's child, for example. Then you have the third level: editing the genes of germinal cells or even embryos. This final level is what people tend to be most concerned about from an ethical standpoint, but this isn't what the vast majority of therapy developers are doing or considering.

"Sometimes the best way to do this is to literally sit with the patient and their family and explain, step-by-step, what each of these levels mean and how their therapy fits in."

What more can you tell me about your work on off-the-shelf stem cells?

In our stem cell therapy program, we're using a new type of cells, called Decidua Stromal Cells (DSCs) to modulate the immune response of patients with graft-versus-host disease. Our pre-clinical and clinical data suggest that the immunomodulatory activity of DSCs is superior to that of mesenchymal stem cells and other therapies.

Decidua stromal stem cells are extracted from the placenta of a woman who has just delivered a baby. These cells play an important role in protecting the fetus from the mother's immune system, but they can't simply block everything – some immune cells are beneficial to the

fetus (or will be beneficial to the baby). So to distinguish between the two, they must be highly specialized in terms of which cells they let through the blood-fetus barrier. In other words, they already have an immunomodulatory role.

We have been working for over three years with a team at Karolinska Hospital in Stockholm, Sweden, which has been exploring the potential of these cells in graft-versus-host disease for almost 20 years. We have already carried out the phase I and IIa studies in Stockholm, and we have an exclusive license for the cells which are now being produced in the US, which means we will be able to conduct phase Iib and III studies in the US. These are off-the-shelf, or allogeneic, cells that we do not (currently) manipulate before they are injected into patients showing signs of graft-versus-host following a bone-marrow transplant. The cells modulate the immune system to prevent the host's cells attacking the transplanted cells.

How should this information be communicated to patients?

Sometimes the best way to do this is to literally sit with the patient and their family and explain, step-by-step, what each of these levels mean and how their therapy fits in. It's especially important to ensure the patient understands they are not receiving a level three therapy – one that would introduce a change into their DNA that could be passed to their children. People may have heard what happened in China, where gene-edited embryos were implanted into two women. People are worried about this – and rightly so. Patients need to understand that this work is not related to their therapy. There may be genuine safety concerns, or risks they should be made aware of, but it should be clear that ethical concerns over "designer babies" aren't relevant here.

I also think patient advocacy groups have an important role to play in bridging the gap between the developers of these therapies and the patient in terms of education.

Are there other stakeholders for whom education is especially important?

It is crucial for the success of the whole field that all stakeholders – especially payers – understand that cell and gene therapies are unlike anything we've seen before. I think everyone appreciates how "cool" these therapies are and, more importantly, understands the value of a potentially curative, one-off therapy. But we need a wider appreciation of how difficult and expensive it can be to produce these products. The cost of goods is uniquely high for cell and gene therapies.

What is the biggest challenge facing cell and gene therapies today?

Some companies are charging $2 million for a therapy, which they say is going to be for life – but how certain can we be about that? The final data on durability is missing: we simply can't know for certain how long a gene therapy is going to last. And, given that uncertainty, how can payers properly evaluate the potential benefit of a therapy? It's a real conundrum we have as an industry – and it's going to be 10–20 years before we have more clarity.

But, even assuming we have good durability, there are challenges surrounding payment and incentives – especially in the US where people often shift healthcare providers when they change jobs. Why should one provider pay $1 million for a curative therapy today when the patient might change jobs and switch to a different provider that would reap the benefits? I don't think this has been resolved. Companies like Novartis are thinking about some kind of insurance pool, but it isn't easy to get competitors to work together – in any field!

What's New from The Cell + Gene Curator?

History made as CAR T comes to China, bad news for Biogen and Tmunity, and the first reported case of partial functional recovery in a neurodegenerative disease after optogenetic therapy… What's new from the Cell + Gene Curator?

By James Strachan

History was made this past month as China's National Medical Products Administration (NMPA) approved the country's first CAR T-cell therapy – Yescarta (1). Born of a joint venture between Kite and Fosun (Fosun Kite), which was established in April 2017, the approval was granted based on the results of a bridging trial, in which 79.2 percent of patients achieved a response after a single infusion, according to Lead Investigator Zhao Wei-li.

It will be fascinating to see how Fosun Kite's pricing, reimbursement, and scale-out strategies compare with what we've seen so far in western markets. One dose of Yescarta costs US$373,000 in the US, but some analysts expect the price to be considerably lower in China. Biotechnology investor Brad Loncar is hearing $150,000 to $200,000, for example (2).

Wang Haopeng, a CAR T expert and professor at the ShanghaiTech University, said: "I suspect they will set a lower price in China because the market will become much more competitive once more domestic companies produce their own CAR T-cell products" (3). He added that some imported drugs in China have lost their market shares because of their high price tags.

Sticking with Kite, they entered into a strategic partnership Shoreline Biosciences to develop allogeneic, iPSC-derived NK and macrophage cell therapies for a variety of cancers (4). Under the terms of the agreement, Shoreline will receive an upfront payment and will be eligible to receive additional payments totaling over $2.3 billion. The news came just a couple of days after Shoreline announced a deal with BeiGene, which is also focused on NK cell-therapy development (5). BeiGene also signed a deal with Strand Therapeutics to develop mRNA-based treatments for solid tumors (6).

Elsewhere, The UK Cell and Gene Therapy Catapult is bringing together over 20 organizations to assess process analytical technologies (PAT) within the cell and gene therapy industry. "The industry needs to make a giant leap in terms of analytical capability and the dynamic use of information to control and improve processes, product and costs," said CGT Catapult CEO Matthew Durdy (7).

"Process analytics is a significant component of the major manufacturing barrier that is preventing the commercialization of therapies for patients," said Jason C. Foster, CEO of Ori Biotech, which joined the consortium (8).

There was some bad news for Biogen, as their phase III gene therapy study in choroideremia failed to meet its primary or key secondary endpoints (9). The experimental therapy was a product of Biogen's $800 million acquisition of Nightstar Therapeutics in March 2019 (10).

"Though we are disappointed by the results of the STAR study, we are hopeful that the clinical insights gleaned from this study may help to shape therapeutic innovation for inherited retinal diseases including choroideremia, so that in the future there may be treatment options for the community affected by these debilitating disorders," said Katherine Dawson, Head of the Therapeutics Development Unit at Biogen.

Tmunity also suffered a serious setback, as the company was forced to shut down their lead program for prostate cancer after two patients died following CAR T-cell therapy. In an interview with Endpoint News (1), Oz Azam and Carl June explained that they were initially shocked at how well the therapy was performing. But the two deaths in the small study forced a rethink.

"What we are discovering is that the cytokine profiles we see in solid tumors are completely different from hematologic cancers," said Azam. "We observed immune effector cell-associated neurotoxicity – ICANS. And we had two patient deaths as a result of that."

"We didn't see this coming until it happened," said June. "But I think we'll engineer around just like we did with tocilizumab back in 2012."

Finally, cell and gene societies were busy publishing advocacy papers over the past month. The Alliance for Regenerative Medicine, EFPIA, and European Association for Bioindustries have called for advanced therapies to be exempt from EU GMO legislation, which they argue hurts

Europe's ability to attract clinical trials and delays patient access (12).

"An exemption from GMO requirements will make the EU a more attractive region for clinical development of gene therapies and could accelerate European patients' access to these potentially life-saving medicines," wrote the coalition in a paper accompanying the press release (13). "Despite recent initiatives coordinated by the European Commission to facilitate and reduce discrepancies across the EU regarding the application of the GMO requirements, it remains particularly difficult to conduct multicenter clinical trials with ATMPs containing or consisting of GMOs involving several EU Member States."

Unproven stem cell therapy is a global problem that requires a global solution, according to three experts. The researchers called for a WHO Expert Advisory Committee on Regenerative Medicine to tackle the issue at the international level and provide guidance (14). "The WHO committee can harmonize national regulations; promote regulatory approaches responsive to unmet patient needs; and formulate an education campaign against misinformation," wrote the Lawrence Goldstein Science Policy Fellows for the International Society for Stem Cell Research.

"People at the conference thought I'd lost my mind."

We had a plethora of research breakthroughs to choose from this month. For example, researchers partially cured a patient's blindness with an AAV-vector encoding algae genes. The international team engineered a light-sensitive protein called ChrimsonR, which is found in unicellular algae, and then inserted them into modified viruses that were injected into one of the patient's eyes. With the treated eye (and while also using engineered goggles) the patient was able to locate, count, and touch different objects. "This is the first reported case of partial functional recovery in a neurodegenerative disease after optogenetic therapy," said the authors (15).

But it's safe to say the research was initially treated with skepticism. "People at the conference thought that I lost my mind to propose to put genes from algae [in] humans," said Botond Roska, corresponding author on the paper in an interview with Salon (16). "Indeed, one participant told me that he hopes that I do not think seriously that this approach will ever be used in humans."

In another interesting early stage study, researchers from UC Davis found that MSC infusions can reduce the amount of the virus causing AIDS, boost the body's antiviral immunity, and repair/restore the gut's lymphoid follicles damaged by SIV, the non-human primate equivalent of HIV (17). The team believes MSCs would nicely complement current HIV treatments. "The antiretroviral drugs can stop the fire of the viral infection but cannot restore the forest of the lymphoid tissue compartment," said Satya Dandekar, senior author of the paper (18). "The MSCs would rejuvenate the field and bring back immune vitality."

Sticking with stem cells, Salk Institute researchers have developed a new and more efficient way to create beta cells, which brought blood sugar under control in a mouse model of type 1 diabetes (19). The team took a stepwise approach, involving a cocktail of chemicals, to produce beta cells from hPSCs. With existing methods, only about 10 to 40 percent of cells become beta cells, but the team were able to achieve yields of about 80 percent.

Researchers from the Keck School of Medicine of USC created collecting duct organoids – potentially a key building block for assembling a synthetic kidney. The team started with a population of ureteric bud progenitor cells, which formed organoids resembling uretic buds – the branching tubes that eventually give rise to the collecting duct system – using a cocktail of molecules (20). They then used an additional molecular cocktail to push the ureteric bud organoids to reliably develop into even more mature and complex organoids that resemble the collecting duct system, which helps maintain the body's fluid and pH balance by concentrating and transporting urine.

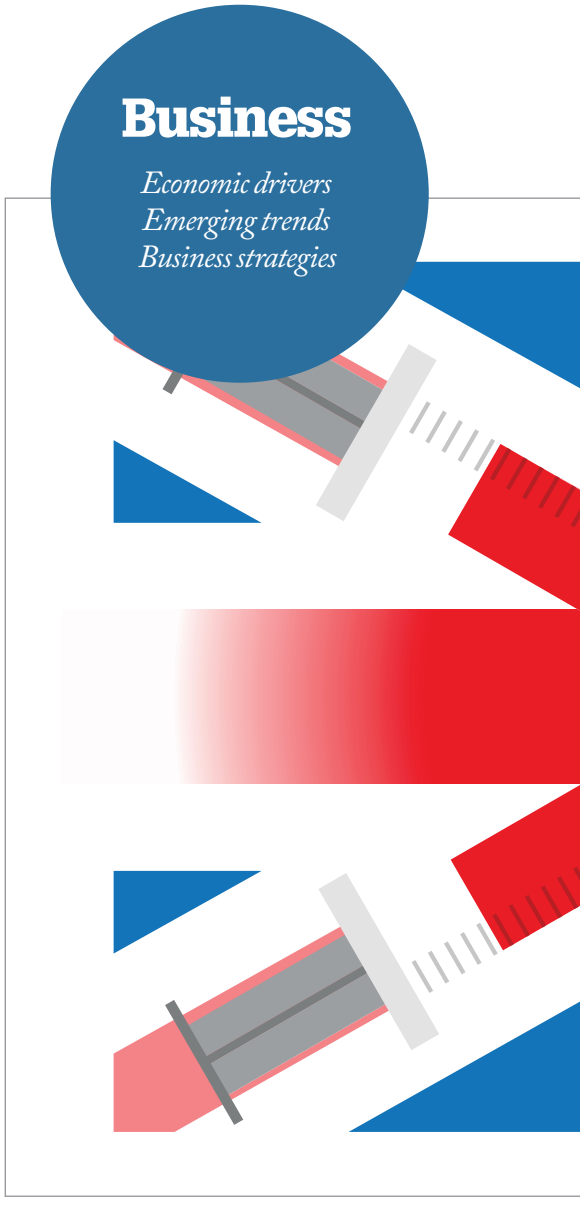
We also saw base editing show promise, as researchers converted the mutated allele that causes sickle cell disease into a non-pathogenic variant to rescue healthy globin production in mice (21). The team, led by David Liu, the co-inventor of base editing and co-founder of Beam Therapeutics, designed a new base editor that can turn a T base into a C, mimicking an ultra-rare, yet functional, hemoglobin variant.

Moving through to an approved gene therapy, Novartis announced positive long-term Zolgensma data. The company's phase III SPR1NT trial shows that all children with spinal muscular atrophy treated with Zolgensma achieved event-free survival, were independent of respiratory and nutritional support, and met the primary endpoint of sitting independently for ≥30 seconds. As the press release points out (22), the results present a remarkable contrast with the natural history of SMA Type 1, which leads to progressive and irreversible loss of motor function and, if left untreated, often results in death or the need for permanent ventilation by age two.

Finally, I thought I'd leave you with a quote from Peter Marks, CBER Director, who spoke at the ISCT's Annual Meeting about potency assays – and what the FDA is looking for.

"The concept of looking at potency as you get late in your process is not working out real well. All too often, people are getting pretty far along, spending millions and millions of dollars in clinical trials, only to find out that when they move to a new manufacturing site [...] they seem to lose a lot or all of their activity. That's a problem. We need to back up some, particularly for cell-based products, and think about potency early on. Perfect is the enemy of good. We may not know what the perfect critical quality attribute is for a product. But pick a few things and measure them – the same way each time. At least this way you've removed some variability."

References available online: https://bit.ly/3kex4VM



COVID-19: Inside the UK's Vaccine Taskforce

Hundreds of millions of doses secured, the first approval, and one of the fastest vaccination programs in the world. How did the UK do it?

As early as June 2020, the UK signed a contract for 100 million doses of the Oxford-AstraZeneca vaccine, and a separate deal securing access to 30 million doses of the Pfizer-BioNTech vaccine was announced the following month. In December 2020, it became the first country in the world to approve a vaccine (Pfizer-BioNTech) for COVID-19. And by June 2021, no country besides Israel had a greater total share of the population that received at least one vaccine dose (58 percent). It's safe to say that the UK's vaccine strategy has been a success.

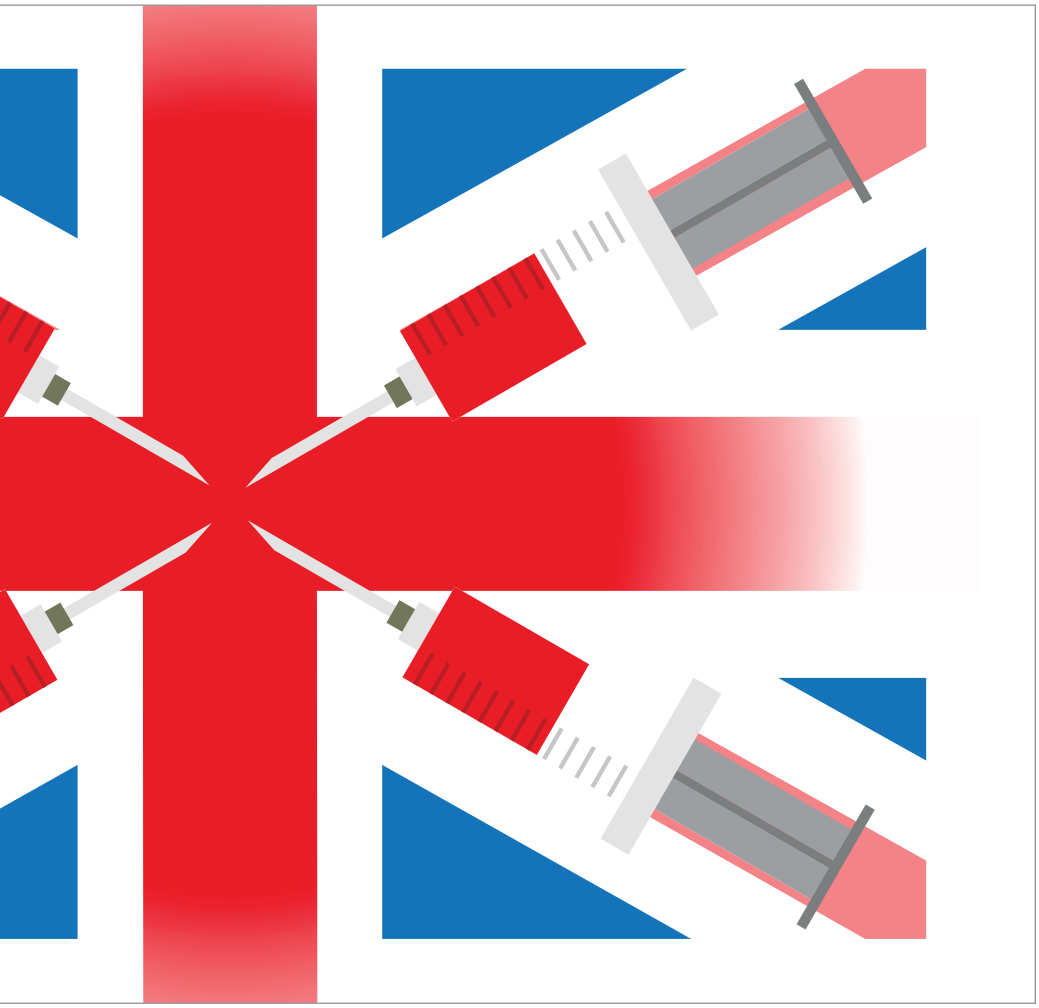
The driving force was the Vaccine Taskforce – led by Kate Bingham – set up in May 2020 to coordinate the UK government's research efforts with industry, academics, and funding agencies to expedite vaccine development and deployment. To get the inside scoop, we spoke with Steve Bates, CEO of the UK BioIndustry Association (BIA), and a member of the taskforce who was responsible for industrial strategy.

What was the main secret to the UK's vaccine success?

In two words: solid foundations. The UK has both excellent universities and excellent companies in biomanufacturing and bioprocessing, which meant that we had an established network of experts who were working on innovation in medicines manufacture in academia and industry going into 2020. At the BIA, we were able to leverage the connectivity that already existed through conferences and the work that had already been done through the technology strategy board and Innovate UK – and then put that expertise to use in developing vaccines. Fast.

So rather than starting with the procurement, we first considered whether we had anybody who could do anything helpful; and, if so, how could we organize their expertise most efficiently? We used the capabilities in the UK ecosystem to help us understand what might work at an early stage. It also allowed us to challenge any claims we were hearing regarding when and how production would proceed. This way, we were able to support academics at the University of Oxford and Imperial College London as early as February 2020, helping them on the journey to scale and manufacture.

In addition to expertise in academia and industry, the UK also has the NHS, which is a healthcare system that knows how to uptake and deliver vaccines at scale – though not at the scale and speed we've seen over the past year! In short, we had the people who knew how to develop, manufacture, and roll out the vaccine with the health service – we just had to ensure everyone was on the same page and working quickly and efficiently together.



What were the main factors influencing the UK's overall vaccine procurement strategy?

There are some fundamental differences between countries that led to different priorities during the pandemic. For a smaller country – for example, Singapore with its population of less than six million – the number of doses required to contain the virus are simply far lower than in a country of 65 million people. There was also a discussion as to whether this is something that should be organized at the country level or as part of a bloc – say at the European level.

The UK could have worked with the EU on vaccine procurement, but it was fairly clear early on that we weren't going to go down that route. Firstly, there was Brexit... But secondly, vaccine procurement wasn't, traditionally, a European Commission competence – these were new tasks for Brussels. There were also difficulties around lending, the practicalities of building and delivering a public good with countries that were at different places with regard to their healthcare systems, and engagement with industry and manufacturing capability. But we knew the UK could do all of these things.

In the end, I think the short lines of decision making and accountability helped

the UK move quickly – and we've seen the impact of that in terms of vaccine doses delivered in the UK compared with the rest of Europe.

Do you think things would have been different if the UK hadn't voted to leave the EU?

It's an interesting historical counterfactual, isn't it? But we'll never know. The UK, historically, wasn't arguing for greater centralization of powers in Brussels. So perhaps, with the UK voice in the room, the EU's vaccine strategy may have been very different. All I can say is that the UK was focused on speed, which was one of the biggest factors when considering who to partner with.

How important was Kate Bingham to the UK's vaccination strategy?

Just as with the UK's overall readiness, overnight successes don't actually happen overnight. Kate has had a fantastic career – including a big Lifetime Achievement Award – understanding and evaluating how to develop therapeutics. She was able to combine an ability to crunch an incredible amount of scientific data with a knack for being able to place bets and weigh up the risks involved. If there was a CV tailored for the task at hand, it was her's. But she's also an inspirational leader. She was able to put together and maintain a team that could work quickly and at scale, while maintaining the confidence of senior government.

The UK had an incredible infrastructure in place. But Kate was able to draw upon her career experience, connections, and goodwill to lead the ecosystem and put it to good use. Her leadership made a big difference.

What has the COVID-19 vaccine development taught the sector?

We've shown that innovation can happen at pace and scale. And it will be harder to make arguments now that we can't do things differently – more quickly, especially. There are other opportunities that have arisen too. Take genomics as an example. The global sequencing capacity is much higher now and this may help us understand disease at the population level. It may also allow us to develop more targeted or personalized therapies. Innovation in healthcare logistics arising out of the vaccine rollout may be applied to surgery. We may also see the advances in mRNA technology made during the pandemic applied to other therapy areas, such as oncology. And perhaps, more generally, there may be a mindset shift towards making sure we target other therapies more effectively as we come out of the pandemic era.

Looking back, how do you reflect on the speed at which the COVID-19 vaccines were developed?

It was quite bonkers! Thinking back to early 2020, it was definitely worth a shot, but it was by no means a slam dunk. There was no certainty and we were taking some big risks. We knew it was a huge challenge, but we had to try. I always had confidence in the community – if it could be done, I knew we had the people with the capabilities to do it.

The UK's Vaccine Timeline

January 2020
- Imperial College London and the University of Oxford begin working on the new coronavirus after Chinese scientists release the genetic sequence of the virus
- The first two cases of COVID-19 in the UK are confirmed

March 2020
- The Prime Minister Boris Johnson announces the first lockdown in the UK
- The BIA forms a COVID-19 Vaccine Manufacturing Taskforce to support Oxford University and Imperial College London's vaccine candidates, chaired by Ian McCubbin, former VP of Global Supply at GSK.

June 2020
- The UK signs a contract for 100 million doses of the Oxford-AstraZeneca vaccine

July 2020
- "I want you to stop people from dying. We need vaccines and we need vaccines to protect the UK," the PM says to Kate Bingham
- Kate Bingham is named to chair the Vaccine Taskforce
- The UK secures access to 30 million doses of the Pfizer-BioNTech vaccine
- The nation begins to ease out of lockdown

August 2020
- The UK government signs deals for 90 million doses of potential vaccines being developed by Janssen Pharmaceutica and Novavax

September 2020
- The UK pledges £500 million to a global vaccine sharing scheme, COVAX

October 2020
- The government takes action to combat rapidly increasing infection rates by announcing a second national lockdown
- Kate Bingham writes an article for The Lancet highlighting the taskforce's overall strategy of a diverse portfolio of vaccines, with an emphasis on those thought capable of achieving an immune response in the over-65s

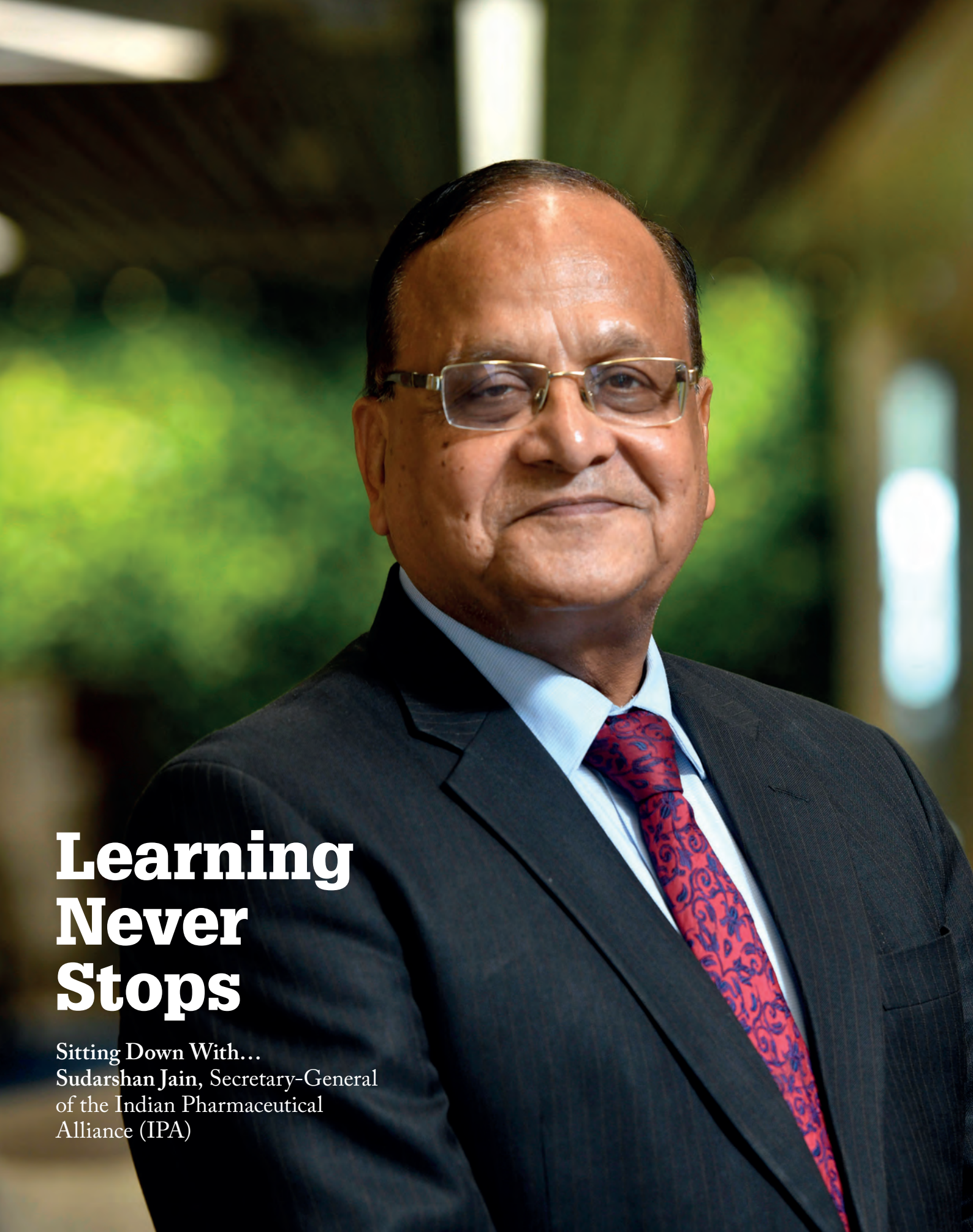
November 2020
- Calls in the UK press to sack Kate Bingham after she "charged taxpayers £670,000 for her own team of specialist PR consultants"
- The Guardian reports that Kate Bingham is "expected to quit"
- "We couldn't understand why our media was doing this at this point when everybody was working their socks off to do something good," said Clive Dix, Vaccine Taskforce Deputy Chair
- Kate Bingham: "If someone had said, 'actually, we spent some money on specialist communications advice, so that we could launch a national citizen registry,' you'd have thought people would say, 'that's actually a pretty good use of spending.'"
- The Pfizer-BioNTech vaccine is found to be 94% effective in those aged 65 and over
- The AstraZeneca-Oxford vaccine is found to be 70% effective, but scientists believe that figure can rise to 90% by tweaking the dosage
- "My two kids and my husband and I were literally dancing around the dining room table" - Kate Bingham
- The UK secures a deal to order five million doses of the Moderna vaccine

December 2020
- The MHRA approves the Pfizer-BioNTech vaccine
- "June Raine of the MHRA really tore up the rulebook of how regulators work [...] she changed the way in which [vaccines] are evaluated," said Kate Bingham
- The second national lockdown ends and England returns to a three-tier system of restrictions, with a fourth tier added shortly afterwards
- Margaret Keenan becomes the first person in the UK to be given the first vaccine dose (Pfizer-BioNTech) following the MHRA approval
- Kate Bingham leaves the Vaccine Taskforce
- "She was the first person to do a deal with Pfizer-BioNTech, she did it with Novavax, she did it with Janssen, she did it with Moderna. And that's why the UK is in a pretty good position. It's not because we elbowed our way to the front of the queue. We were at the front of the queue to start with," said John Bell

January 2021
- England enters third national lockdown
- UK first dose vaccinations reaches 3,500,000
- "I cannot wait for the next year to see how many people now take part in cancer studies, diabetes studies, asthma studies, because I think this has set a benchmark for future research," said Divya Chadha Manek

April 2021
- UK tabloids argue that backing several COVID vaccines seems to be paying off following Janssen's decision to delay the supply of its COVID-19 vaccine to Europe. "That reflects well on the decisions taken by the Vaccines Taskforce, originally headed by Kate Bingham."

Source
Channel 4, "Jabbed! Inside Britain's Vaccine Triumph" (2021). Available at: https://bit.ly/3vTySGD



Learning Never Stops

Sitting Down With…
Sudarshan Jain, Secretary-General of the Indian Pharmaceutical Alliance (IPA)

How did you get started in pharma?

I've worked in the pharmaceutical industry for over 40 years, but my early career path wasn't conventional. I didn't have a background in biological sciences. In fact, I had pursued a bachelor's degree in physics at St. Stephen's College, Delhi, and an MBA soon after. Though I had chosen this academic route, I did have a keen interest in healthcare and pharma. These industries do, after all, make a huge difference to patient lives worldwide. But the reason I happened to join the industry was due to a chance meeting.

I was lucky enough to meet Desh Bandhu Gupta, owner and founder of Lupin Pharmaceuticals, during my business administration degree. He came to my campus to find young professionals interested in helping him develop his ambition of creating one of the world's largest pharma companies for tuberculosis treatments. At the time, I was industry-agnostic – more interested in building an interesting career than pursuing a particular therapeutic area. But my meeting with Gupta was inspirational. He was the type of person who encouraged people to think big and to put patients first. His ideas and conviction were what convinced me to join him. I spent over three years with the company, learning and growing, before moving on to a role at Johnson & Johnson.

Which of your career milestones are the most important to you?

There isn't one particular moment that stands out to me, but there have been many lessons learned. At J&J, I helped to develop their diagnostics business in India before moving on to other companies and therapeutic areas, such as over-the-counter medicines and healthcare products. I've been involved with a lot of product categories over the years and have come to enjoy the challenges and rewards that come with new markets and working alongside professionals from across the globe.

But the most important lesson echoes from all my bosses, "through it all, the patient has to come first." If you understand patient needs, obtain specialized insights, and develop therapies using a patient-centric approach, your company's work will always be in demand. It has also been a pleasure to work alongside individuals committed to developing markets on sound, ethical footing. I've met so many outstanding people who are passionate about making a difference and lead many of India's pharmaceutical companies today. So, those have been the best parts!

How did you get involved with the IPA?

I've always been interested in the IPA's activities. They are a leading association in the country, and its members contribute both to India's domestic and export markets. Its former Secretary-General, D.G. Shah, was a prominent voice in the Indian pharmaceutical community, but after his unfortunate demise, I was invited to assume the role, which I've held for over two years. Since then, I've worked alongside industry and government to help align pharmaceutical strategies within and outside of the country.

What are your goals for the next five years?

India is known as the pharmacy to the world. We supply medicines to 200 countries worldwide and every third tablet sold in the US comes from here. Although we play an important role in the distribution of drug products to the global market, I would like to see an increased focus on drug discovery within our own borders. We should be able to deliver our own chemical entities alongside other drugs to our international partners and customers. At the IPA, we are working towards creating an ecosystem where India can thrive as an innovation hub. I'm excited to see this come to reality.

But at the same token, we must maintain a diversified supply chain that fosters competitiveness. Though some suppliers may have the capacity to manufacture particular products, if they unexpectedly run into issues, then everyone is affected. Although it is important to manufacture drug products domestically, we owe it to our citizens to ensure that multiple, diverse supply chain submissions are available to meet their needs.

What has the IPA taught you?

At the IPA, our ethos has three focus areas: innovation, quality, and reach. The COVID-19 pandemic has truly highlighted the importance of these values as we work alongside the government to maintain supplies of essential medicines. Despite the challenges that the crisis has and continues to bring, we have consistently met with suppliers and worked with industry leaders to distribute medicines of consistent quality and think of new ways to approach problems, we hadn't faced previously. In my view, the IPA provides an environment where all pharmaceutical stakeholders can work together to push forward a positive healthcare agenda. Each day is a new learning opportunity, whether that be on the intricacies of domestic government policies or the impact of geopolitical situations on our industry. I'm grateful to be a part of such an open-minded community where the value of continued learning is held in high regard.

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