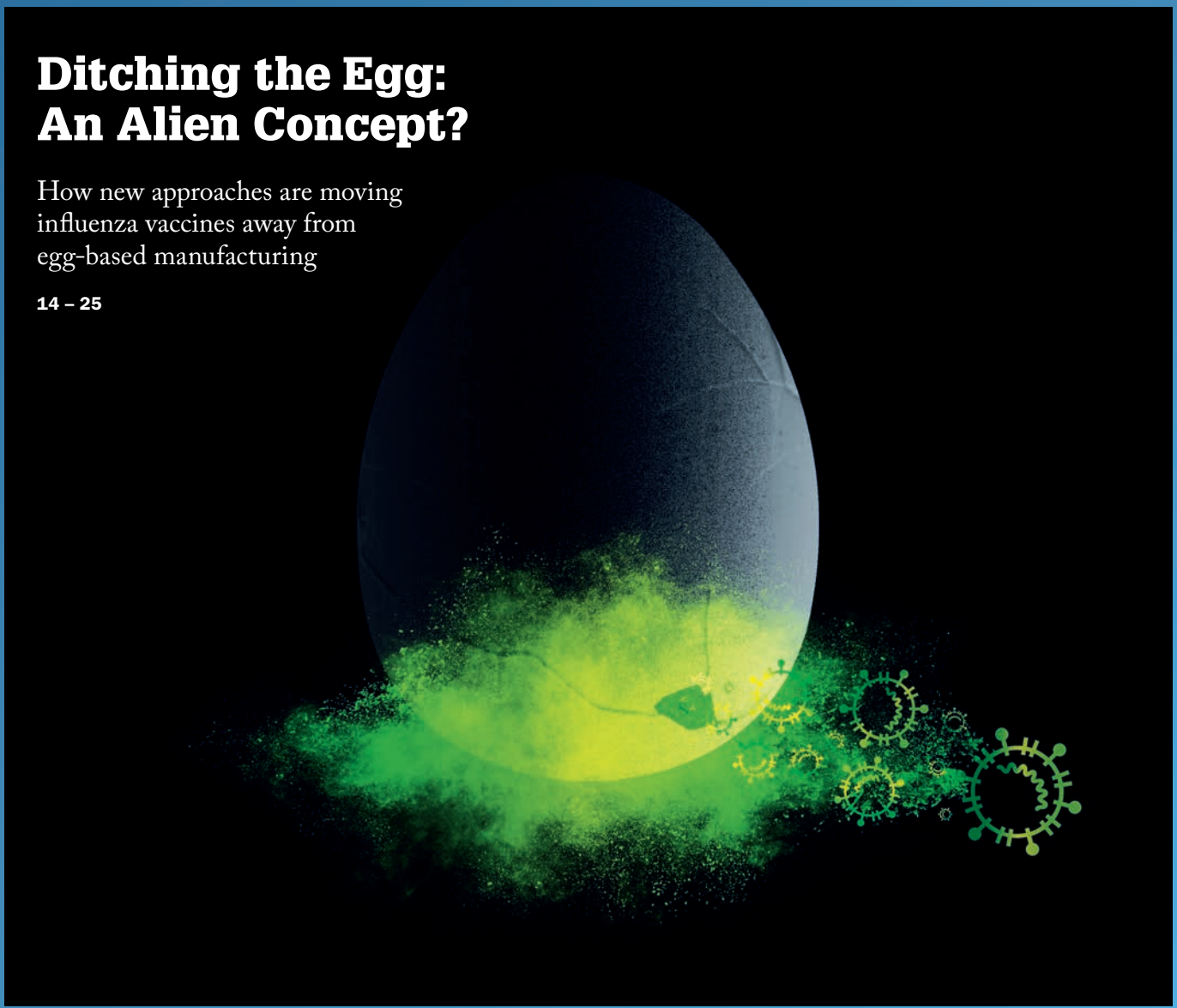
JANUARY / FEBRUARY 2023 # 89

the Medicine Maker®

Ditching the Egg: An Alien Concept?

How new approaches are moving influenza vaccines away from egg-based manufacturing



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Abortion Lawsuit Headaches

Kicking off with controversy – welcome to 2023

After the US Supreme Court ruled last year that access to abortion is not a constitutional right, it was inevitable that pharma companies with FDA-approved drugs would react. GenBioPro – manufacturer of generic mifepristone – has filed a lawsuit directed at West Virginia state's ban on abortion medicine.

Abortion is, of course, a contentious issue and personal views on the matter quickly heat up. But I'm not writing this piece to discuss whether abortion is right or wrong; for me, the provocative question raised by the GenBioPro lawsuit is: What happens if courts decide that individual states can overrule access to an FDA-approved medicine? Allowing states to pick and choose which FDA approvals to respect or deny could have huge implications for patients, regardless of their views on abortion.

And this isn't the first time GenBioPro has tried to sue a state over access to mifepristone; the company challenged Mississippi last year but then dropped the case without giving details as to why – other than saying it had decided to adjust its strategy.

Since the overturning of Roe v. Wade, the FDA made changes to the labeling of abortion pills, which means they can be sold by more pharmacies, including large chains and mail-order companies. The change allows women to access abortion pills even if they live in a state that limits abortion. Many have welcomed the labeling update, but those with pro-life views are furious.

The Alliance Defending Freedom (a conservative Christian legal advocacy group) accused the FDA of caring more about "forwarding a destructive agenda" than protecting women and children. The group is leading a lawsuit that seeks to declare the FDA's approval of abortion pills as unlawful. At the time of going to print, a decision from a Texas judge on the matter was due any day – a decision that could have implications for US-wide access to mifepristone.

And there's still more. The FDA is also facing a lawsuit from the other side of the fence, with 12 liberal states claiming that limits on mifepristone are still too strict, even with the recent labeling changes. This lawsuit is nicely timed with the decision in Texas – unlikely a coincidence; conflicting rulings will force the Supreme Court to step in.

Whatever the outcome, I can't imagine either side backing down quietly.

Stephanie Sutton
Editor

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On The Cover

In a vaccine production facility no one can hear you scream

the Medicine Maker

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Credit: Henk Monster / Wikipedia

Memorable Mushrooms

These fungi have some real nerve (developing properties)

With the pharmaceutical industry still eagerly awaiting positive results from ongoing Alzheimer's drug trials, perhaps the search for an effective – and sustainable – treatment needs to extend into the dark, damp places preferred by fungi. In fact, extracts from the lion's mane mushroom (Hericium erinaceus) have been used in traditional medicines for centuries, but scientists from the University of Queensland, Australia, and Chungbuk National University and Gachon University, South Korea, are now investigating the compounds for potential applications in Alzheimer's treatment (1).

Tests have shown that certain compounds from the mushrooms could potentially improve memory in both rats and humans, although scientists have not yet pinpointed the exact compound or combination of compounds. The lion's mane mushroom contains, in its edible parts, both hericenones and erinacines, which the research team says are linked to brain cell growth and memory improvement. Lead author of the paper, Frédéric Meunier, Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, Australia, said, "Using super-resolution microscopy, we found the mushroom extract and its active components largely increase the size of growth cones, which are particularly important for brain cells to sense their environment and establish new connections with other neurons in the brain."

Further evidence suggests that the active ingredients could also help brain cells live longer, hence the interest in Alzheimer's treatment. According to the researchers, a Japanese study from 2009 showed similar results in people aged 50–80 who were diagnosed with mild cognitive impairment (2). Those participants who took lion's mane mushroom extracts three times per day for 16 weeks exhibited significant improvement in cognitive function compared with a control group. Tests continued after the 16 week intake period and showed a subsequent decline in cognitive function.

Is there a future in lion's mane compounds in Alzheimer's treatments? Well, I don't think there's mushroom for debate (sorry).

References

1. *F Meunier et al, 'Hericerin derivatives activates a pan-neurotrophic pathway in central hippocampal neurons converging to ERK1/2 signaling enhancing spatial memory', J Neurochem, [online ahead of print] (2023). DOI: 10.1111/jnc.15767*
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INFOGRAPHIC

Here Come the Humira Biosimilars

Twelve biosimilars to Humira are expected to launch in the US in 2023

Source: Goodroot, Breaking Down the Hottest Topic in pharmacy - Humira Biosimilars (2023).

Key predictions

- **Humira likely to be preferred on formularies for 2023**
- Biosimilars expected to gain up to 5% market share by end of year; maximum of 20-25% market share by 2026

Companies expected to launch biosimilars to Humira in 2023

Sandoz
Pfizer
Amgen
Boehringer Ingelheim
Samsung Bioepis/ Organon
Mylan/ Biocon/Viatris
Celltrion
Coherus BioSciences
Freesenius
Alvotech/ Teva

RESEARCH-IN-BRIEF

Here's some fascinating early-stage research we've spotted in academia

Credit: Wikipedia

- Harvard spin-off CELLVIE has raised $55 million in additional funding to develop mitochondria transplantation into compromised cells as a new treatment modality. The company hopes to one day have an allogeneic product, but is also researching the potential of the modality in gene therapy delivery. Mitochondria dysfunction has been tied to numerous diseases.
- Machine learning models have been used by scientists at the University of Toronto to guide the design of polymeric long-acting injectable drug formulations (P Banngan et al.; DOI: 10.1038/s41467-022-35343-w). The team trained eleven different AI models, with light gradient boosting machine (lightGBM) delivering the most accurate results when the team compared the predictions from the model against real-world experiment data.
- More on AI – this time from the University of California San Diego. AI has been used to identify a new antibody that binds to a major cancer target 17-fold tighter than existing antibody drugs (J Parkinson, R Hard, W Wang; DOI: 10.1038/s41467-023-36028-8). The research team is now using their algorithm to identify antibodies against SARS-CoV-2, and developing new AI models that analyze amino acid sequences to predict factors such as solubility and stability.
- Researchers in Texas investigating dolphin kidney stones believe their work on manipulating tautomers and controlling the growth of ammonium urate crystals could also be applied to humans (W Tang et al.; DOI: 10.1038/s41467-023-35924-3). Drugs that are tautomers can develop defects, which can affect how fast they dissolve and take effect in the body. A process to control this could offer benefits.

Pfizer's Record Revenue

How much further can COVID-19 products carry the company?

Revenues have reached an all-time high for Pfizer: $100.3 billion in 2022 (up by 23 percent compared with 2021), buoyed by its COVID-19 products Paxlovid and Comirnaty. But is the company's golden era coming to an end as demand for COVID-19 vaccines starts to wane? For 2023, the company is expecting revenue of around $67-71 billion; sales of Comirnaty are expected to slide by 64 percent, while Paxlovid will drop by 58 percent.

In a statement, the company said, "In contrast to previous years, guidance for both products is no longer based primarily on expected deliveries under existing signed or committed supply contracts, but now also includes, among other things, anticipated sales through traditional commercial markets in the US in the second half of 2023."

Excluding revenue from Paxlovid and Comirnaty, Pfizer's revenues grew 2 percent operationally compared with the previous year.

Key Humira dates

2002 FDA approval

2012 Becomes the best-selling drug in the world with $9.3 billion in global sales

2016 Patent expiration. Litigation commences to potentially delay biosimilars

2018 New high-concentration formulation launched

2021 Accumulates more than $200 billion in total revenue; drug becomes world's all time biggest seller

2023 Market opens for biosimilars

The Blood Clot and the Invisible Frog

What do tiny glass frogs have to do with medicine?

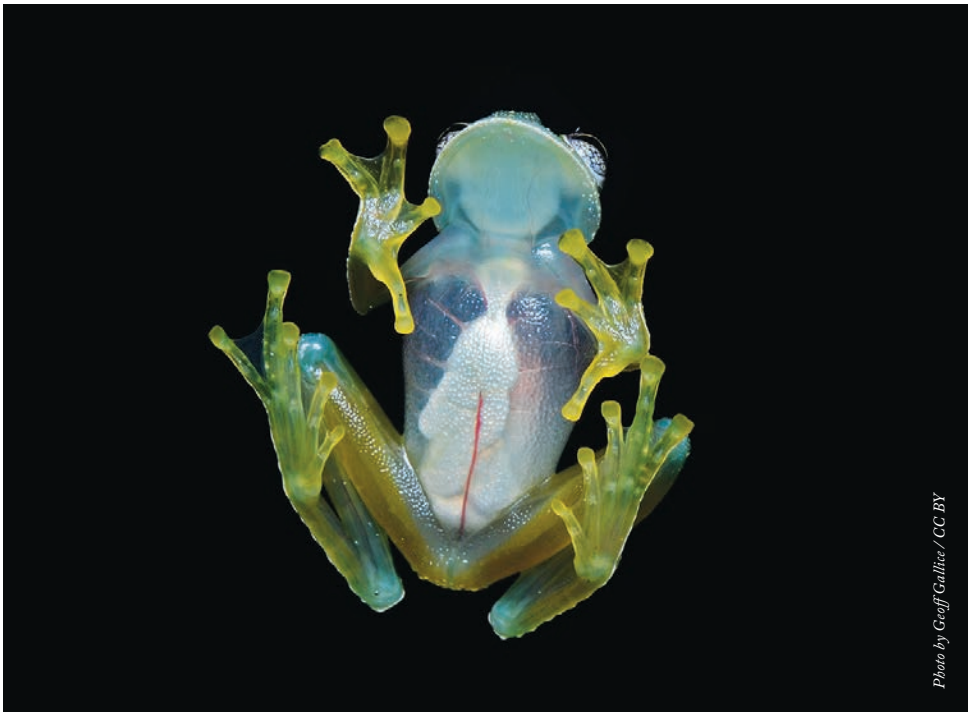

Photo by Geoff Gallice / CC BY

Just as H. G. Wells' Invisible Man found a way to alter his body's refractive index and render almost every cell* in his body unable to either reflect or absorb light, groups of tiny glass frogs can sleep on a leaf in daylight and go entirely undetected by predators. The glass frog is active at night, during the day – when predators abound – it is dormant, hence its need for superior camouflage. Like the Invisible Man, the glass frog is unable to make all of its cells "invisible" – with its red blood cells being spectacularly stubborn (Wells' protagonist encountered the same issue, but overcame it through the use of "bleach"!). And yet the frog appears to disappear, so where does it hide them? In its liver, according to Duke University researchers Jesse Delia and Carlos Taboada (1).

By redirecting most of its red blood cells (~89 percent) into its liver, which doubles in size, it gets a little closer to the Invisible Man, increasing its transparency two- to threefold. But with so many red blood cells packed in such close proximity, how does it prevent coagulation?

This excellent question has prompted interest from the drug discovery world. Perhaps the impossibly delicate glass frog holds the secret to anticoagulant medicines for those at risk of venous thromboembolism (VTE). According to the CDC, VTE affects up to 900,000 people in the US alone each year, causing sudden death in one in every four (2).

Extensive research into the glass frog and its extraordinary ability looks set to continue. Now, where did I put that specimen…

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1. *C Toboada, et al, 'Glassfrogs conceal blood in their liver to maintain transparency', Science, 378, 6626 (2022). doi/10.1126/science.abl6620*
2. *CDC, 'Impact of Blood Clots on he United States' (2022). Available at: https://bit.ly/3VKRy7A*

** "I went and stared at nothing in my shaving-glass, at nothing save where an attenuated pigment still remained behind the retina of my eyes, fainter than mist."*

In Africa, For Africa

Project MADIBA is on a mission to improve health equality

CEPI is creating a network of vaccine manufacturers with the aim of substantially increasing the capacity and capability of producing vaccines against emerging endemic and pandemic threats. One of its latest announcements is a new, 10-year partnership with the Institut Pasteur de Dakar (IPD), which has manufactured yellow fever vaccine antiamaril since 1938. IPD will also contribute to CEPI's ambition of bringing improved health equality for countries in the global south by becoming a regional manufacturing hub.

Through Project MADIBA (Manufacturing in Africa for Disease Immunization and Building Autonomy), IPD will receive up to $15 million in grant funding over three years – and this figure could rise to $50 million over 10 years should they wish to expand the partnership. CEPI's investment will complement that of other major funders, including the EU, European Investment Bank, the Agence Française de Développement, the Islamic Development Bank, and the US International Development Finance Corporation, amongst others.

IMAGE OF THE MONTH

Cell and Gene Go Large

The Cell and Gene Therapy Catapult's estimated 1.4 million square feet of laboratory and office facilities could provide up to 5,000 new UK jobs

Credit: The Cell and Gene Therapy Catapult

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QUOTE of the month

"Biopharma is not an easy industry. We are faced with constant challenges, failures, and setbacks on a regular basis as part of the scientific process. We have to make sure that we are kind to ourselves and do not let the negativity get us down."

Eric Dube, CEO, Travere Therapeutics. Read more on page 50.

Pharma Sets Sights on Ireland

AstraZeneca turns its eyes to Dublin

A new AstraZeneca factory in Dublin, Ireland, is expected to create around 100 skilled jobs. (AstraZeneca currently employs around 80 people in the country, mainly in administration or sales capacities).

The big pharma company reportedly expressed concern about building a new plant in the UK because of its discouraging tax rates, and evidently chose to invest in Ireland instead. Speaking to the media, ABPI CEO Richard Torbett said, "Companies are now paying more than a quarter of their revenues – not profit but revenues – back to the [UK] government."

The new facility – to be located at the 41 acre Alexion Campus in College Park, Dublin – will focus on API commercialization as well as manufacturing small molecules pharmaceuticals.

In My View

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

Chill Out: Understanding the Realities of mRNA Therapeutic Storage

Are glass syringes suitable options for mRNA therapeutics?

By Silvia Gallina, Product Management Specialist at Stevanato Group and Marco Povolo, Senior Research Analyst at Stevanato Group

The COVID-19 pandemic was undoubtedly challenging for everyone. We all know that the COVID-19 vaccines have been a success, but less appreciated is the role of drug containment solution providers. Alongside their regular activities, these companies had to deliver glass vials to industry – helping to ensure that the billions of doses of COVID-19 vaccine could be easily delivered to patients worldwide.

As with many other companies in the pharma industry, glass containment manufacturers also encountered mRNA technologies for the first time. mRNA-based COVID-19 vaccines required cold chain storage to maintain their stability, so containment providers had to provide primary packaging that could work in extreme conditions. Having limited data and experience of working at such low temperatures added some challenges, especially concerning container closure integrity (CCI) and mechanical performance of the glass.

In our view, packaging developers have learned many important lessons during the COVID-19 pandemic, but one of the most important lessons relates to the understanding of the performance of primary packaging glass containers at low temperatures. Companies had to critically evaluate the suitability of glass containers by identifying the critical and quality attributes for different types of containers. This required extensive technical support and testing as well as a close cooperation with the customers.

As we move from the height of the pandemic to the endemic phase, the number of COVID-19 vaccine doses administered will certainly drop. This, alongside the need for improved dosing and waste reduction, will push glass providers to move from vial to syringes supplying for mRNA vaccine applications.

Syringes are already present as containment solutions for a variety of medical products including interventions like flu vaccines.

Today most vaccines are commercialized in vials due to the high flexibility they offer during the drug development phase and their speed to market. However, when considering lifecycle management, a migration to pre-fillable syringes (PFS) has several advantages over vials in vaccine delivery. Lower dead volumes, a reduced risk of dosage errors, shorter injection times, and decreased risk of injury during vaccine administration are all possible using this drug delivery format.

But will glass syringes meet the challenges of deep-freezing conditions? Companies will have to apply their learnings from the early days of the pandemic to ensure that syringes can meet the containment requirements of mRNA-based vaccines. One major consideration is container closure integrity (CCI) and the ability to maintain a sterile environment. Companies will need to ask themselves how they can avoid the loss of sterility, as mRNA products go through the freezing and thawing cycles that come with cold storage.

There are several key considerations that companies will have to make to ensure they can reduce risk. First, companies must assess how drug freezing affects plunger movement. Water-based liquids expand when frozen. In a syringe this results in a lateral force moving the plunger towards the flange. The headspace between the plunger and the dose tends to reduce in volume during cooling, cause the plunger to suck inward. As they develop novel syringes, they will have to take issues like this into account.

Second, it is important to test contraction of air during the freezing process. Plunger movement can be observed more for empty syringes and less for filled syringes, likely due to the difference in compressible air volume. This may lead to the recommendation to either adopt an airless filling process or maintain the amount of air between drug and stopper to a minimum level. Adopting an airless filling process or maintaining the amount of air between drug and stopper to a minimum level should help companies avoid this problem.

Third, companies must examine plunger stopper shrinking and change of material properties impairing seal integrity. Here, two factors must be considered. The mismatch of the coefficients of thermal expansion (CTE) of glass versus rubber can cause them to shrink at different rates at low temperatures; and the rubber exhibits a glass transition temperature close to the target temperature that could change the mechanical properties from a viscous/rubbery state to a harder and more brittle one. A solution would be to aim to create rubbers with lower glass transition temperatures or with CTEs similar to the glass.

With these considerations made, companies will be armed with the information to produce better, more efficient primary packaging for their products. The mRNA therapeutic market is growing and the technology will certainly be a part of the future pharmaceutical landscape. It is more than likely that we will see its use expand beyond infectious disease and into other therapeutic areas like oncology. As this happens, packaging providers will have to create the containment solutions that allow this particular segment of the pharma market to thrive.

Connected Patient-Centricity

How digital health technology can help clinical trials be more inclusive and accessible

By Oliver Eden, Business Unit Director, Jabil Healthcare

When deployed strategically and designed with intention, healthcare technologies excel at solving delivery challenges and pushing back on traditional boundaries. Clinical trials are shifting towards a decentralized structure, thanks to digital technology's potential for improving data collection, enrollment, and participation metrics. They also provide powerful methods for expanding diversity in methodologies, geographies, and populations. Though the COVID-19 pandemic accelerated the shift from traditional research practices to hybrid or decentralized clinical trials (DCTs), it is the resulting improvements and expansions in patient engagement that support longer-term momentum.

Today's digital healthcare technology offers study sponsors a highly effective toolset for the centralized acquisition of data to support their study's defined scientific endpoints. A drug delivery device that can capture and report accurate, objective data is an obvious improvement over manual self-reporting. However, self-administration in the home setting can be challenging simply due to limited oversight and the fact that human beings can be unpredictable when dealing with program instructions – not to mention potentially unfamiliar technology. Just as drugs don't work in patients who don't take them, digital health technologies won't deliver value if patients can't use them.

As a manufacturing solutions provider of smart, connected systems in pharmaceutical delivery, Jabil engineers prioritize patient-centricity in device design, often weighing the balance between the benefits of digital features and the capabilities of the patient population. Recently, when developing a reusable autoinjector platform, the Jabil product team asked, "What is the best way to fully harness the device's data-capture capabilities with the smallest burden on patients?"

We had the challenge of developing the product with a smartphone app as the communication method; however, as we investigated the typical application of the device, we realized that our patient demographic was mostly 55 and older and typically had other medical challenges. This group are also the most technically challenged and have the poorest smartphone penetration, which means we needed alternatives.

Currently, many market-leading autoinjector platforms require smartphones

for data transmission. Though seemingly convenient, smartphone penetration varies significantly by geography, demographics, and socioeconomic status. Even in an advanced country like the US, smartphone penetration in over-65s – a key market for healthcare – is only 61 percent, according to research from PEW. Throughout the developed and developing world, coverage gaps exist and must be considered.

From a patient-centric perspective, consider these limitations to smartphone-required connectivity:

- More involved initial training required for participants and caregivers.
- Study investigators and participants must download a smartphone app and be competent at pairing their device.
- The autoinjector and smartphone must be co-located for data transfer.
- Smartphone ownership becomes an inclusion criterion in the study design – or one must be provided by the sponsor.
- Technical troubleshooting must be timely, responsive, and "on call" throughout the study period.
- Each time the patient interacts with the app (to push data to the smartphone), it becomes an overt reminder that they are being monitored, impacting patient behavior.

This final point is particularly challenging because it introduces bias to the patient population. Together, these challenges raise the potential for additional study costs or time to complete enrollment, as well as the potential for limiting the demographic and geographic diversity of study populations. At a time when clinical trials strive to be more inclusive, the benefits of technology should not be prioritized over simplicity and inclusion.

"By 2025, 75 percent of trials will be patient-centric DCTs; 90 percent of those will be hybrid and at least 10 percent will be virtual."

Innovation has the chance to dramatically improve studies through collection of richer, more robust data – but, if the technology solution is not available to all, it limits enrollment and risks stratification in the data. For a connected autoinjector to deliver on its promise, it does not need hard-to-read touchscreens, smartphone apps, or other interface features that will require additional training for the patient or caregiver and ongoing IT support.

Our engineers determined that the most patient-centric option would be data transmission via cellular networks, which offers exceptional accessibility with greater than 95 percent coverage globally. But what is the easiest data transmission trigger? We settled on a docking station for after-use storage of our connected autoinjector.

Both the connected and non-connected versions of the autoinjector platform are intentionally designed to look and feel the same, with the connected version's electronics integrated into the same form factor. In other words, users of either version follow the same steps and grip function without requiring additional training. The connectivity benefit is fulfilled simply by placing the device back into a "home hub" docking station that initiates the automatic transfer of injection event data and charges the device for its next use.

A typical drug trial can take more than a decade and cost over a billion dollars, with many failing to meet enrollment timelines or terminating due to participation challenges. It's more important than ever to make sure your trials are as accessible as possible. As part of diversity research in clinical trials, Pfizer recently reported that Black Americans make up 13 percent of the US population, but just 5 percent of clinical trial participants – and the gap is even worse for Hispanic or Latino Americans. After decades of low representation, government bodies and trial managers are determined to expand participation diversity.

Research from IDC predicts that, by 2025, 75 percent of trials will be patient-centric DCTs; 90 percent of those will be hybrid and at least 10 percent will be virtual, driven by 30 percent growth in connected health technologies. Separately, McKinsey reports that 89 percent of participants in their Clinical Operations Roundtable expect to run a trial with most activities conducted in participants' homes.

Although innovation is critical to digital healthcare, it's also important that pharma companies and device manufacturers not leapfrog their patients' ability to use technology. Will a patient's experience with the device be easy and familiar? Will they be able to figure out device protocols intuitively or are they facing an uphill battle with a 30-page, fine-print IFU document? Whatever innovations may be embedded into a particular delivery solution, form should serve function. Or, put another way, if you do well by the patient, you will do well by the science.

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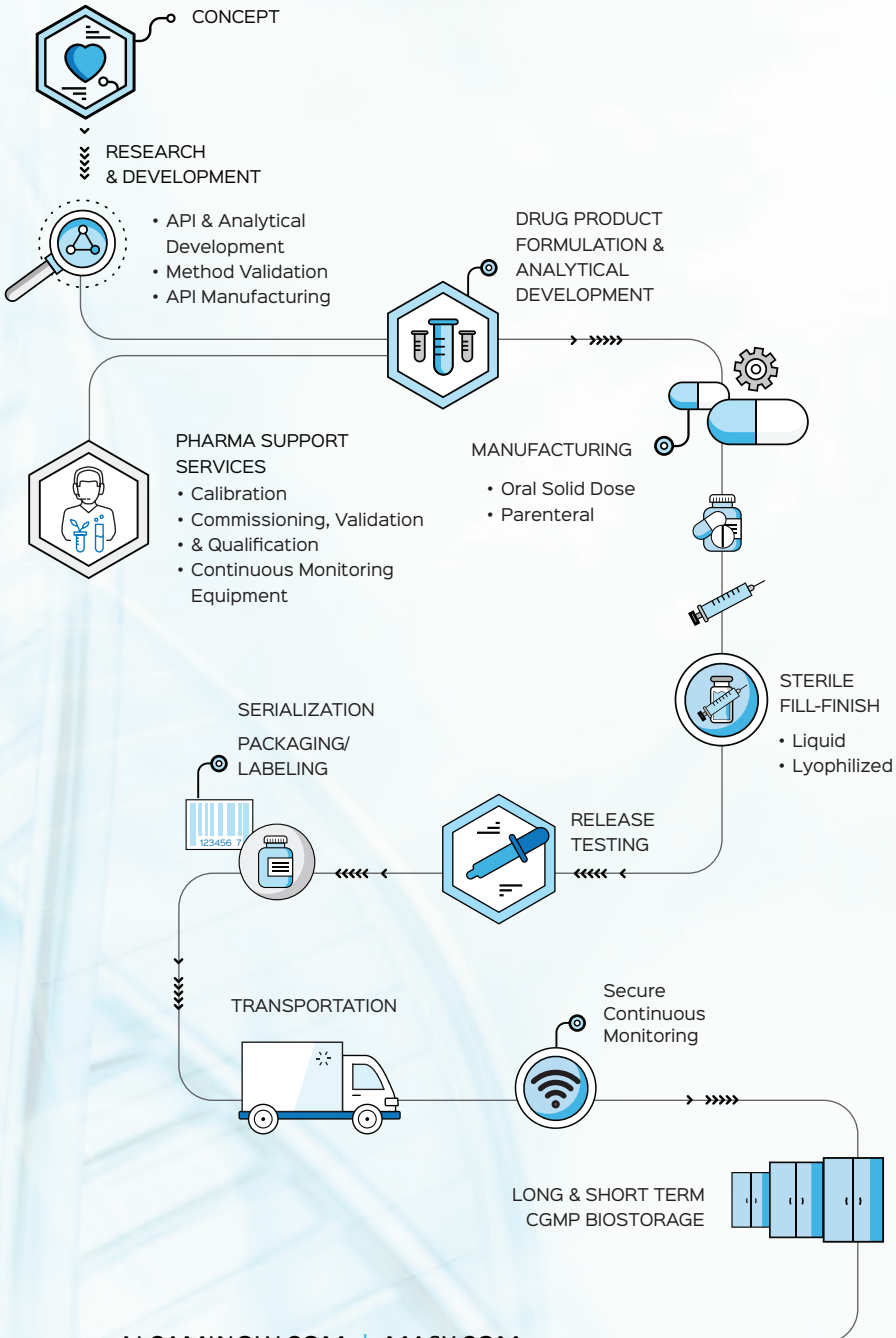

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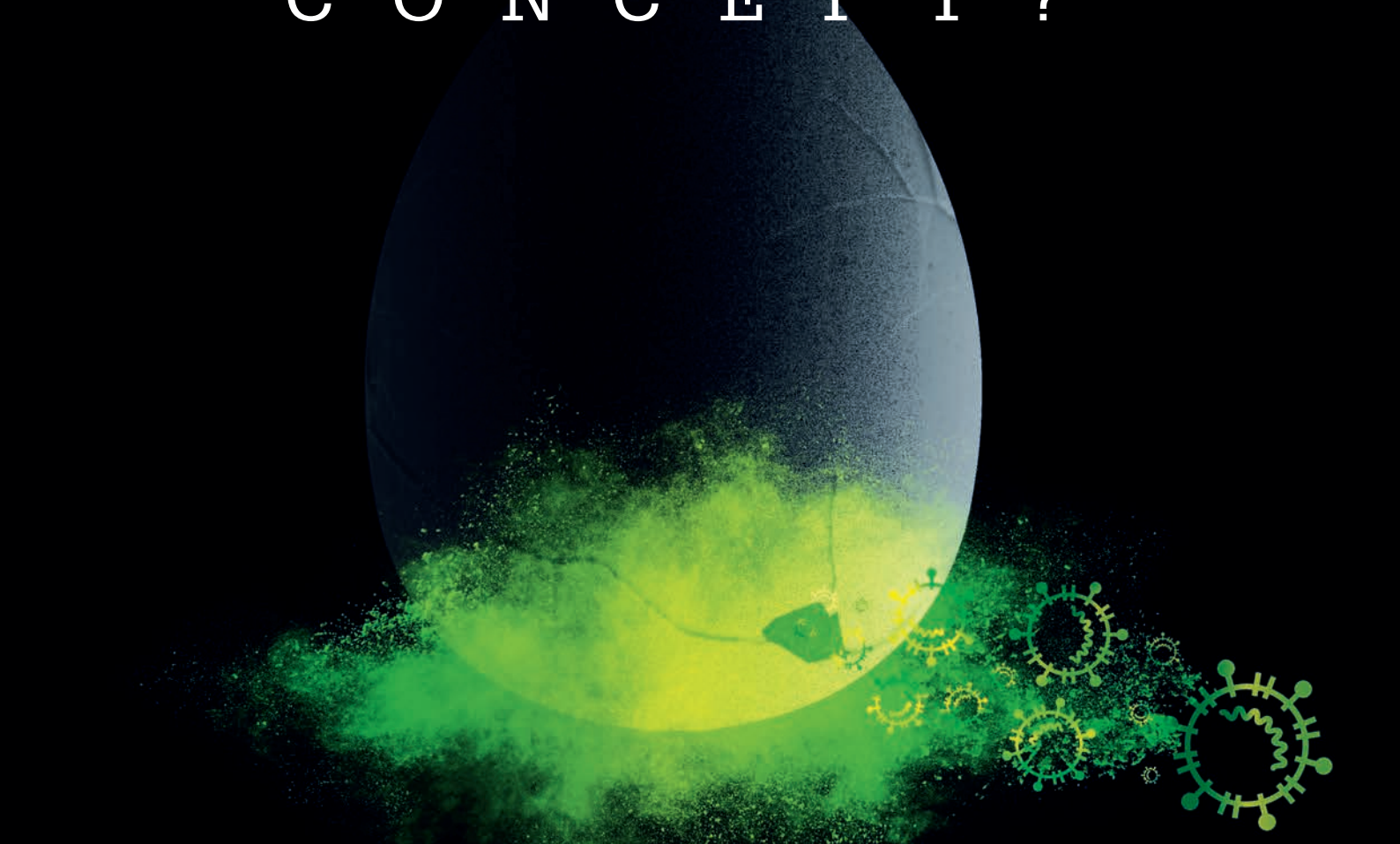
DITCHING THE EGG: AN ALIEN CONCEPT?



When it comes to influenza, chicken egg-based vaccines have achieved much, but emerging approaches are ready to fly the coop – and they might just be something to shout about

By Stephanie Sutton and Rob Coker

"In a vaccine production facility, no one can hear you scream."*

*OK, they probably can, but where else can we use such an iconic sci-fi movie reference?

As many of you will know, the vast majority of influenza vaccines are traditionally made in chicken eggs. The virus is grown in the chorio-allantoic membrane which surrounds the embryo of a fertilized egg in a well-established process that has been used for decades. Prior to COVID-19, vaccines were not a hot topic, nor were they frequently seen as a lucrative business prospect. It was well accepted that more modern processes could be used for influenza vaccine production, but innovation in this space has been slow for a variety of reasons, including the old adage: "If it ain't broke, don't fix it (especially if the latter needs investment)."

That said, some companies were starting to evaluate other options, including a shift from egg-based to cell-culture-based vaccines. One example of innovation in this field is Flublok – a protein-based vaccine made in insect cells. According to Piergiuseppe Nestola, Manager of Process Technology Consultants at Sartorius, the influenza vaccine has always been a key vaccine to optimize and improve, particularly in terms of the manufacturing process. "Egg-based processes are slow and require huge facility footprints, which are also becoming unfavorable as more attention is paid to sustainability. In terms of development, strain selection is a challenge too. There is a limited window of time from when the yearly influenza strain is detected, which puts pressure on the process. It's not unusual in influenza for the strain selected to ultimately not end up being the one circulating with high prevalence during the winter seasons."

Explaining one of the biggest disadvantages of traditional egg-based processes, Joseph Payne, CEO, President, and Co-Founder of Arcturus Therapeutics, which is developing mRNA-based vaccines and therapeutics, points to another element of speed. "The term in the vaccine industry that is extraordinarily important is 'clock speed.' The World Health Organization (WHO) and other non-profit organizations will publicly share the strains of concern – and then vaccine producers design, manufacture, and distribute the vaccine in time for the flu season."

Recognizing the challenges, some companies were already taking action. The famous Pfizer/BioNTech COVID-19 vaccine actually has its roots in influenza innovation efforts, with the companies agreeing their first partnership in 2018. In 2020, the companies agreed to expand their collaboration to the far more pressing threat of COVID-19. The story of the COVID-19 collaboration is history, but what of influenza? The work continues – with volunteers recruited for a phase III clinical trial last year. Ultimately, they hope that an mRNA-based method will be faster to develop and manufacture, thus achieving more accurate matching against circulating strains.

Several companies are now keenly exploring the potential of mRNA. One key area of interest is combining influenza and COVID-19 vaccines in a single shot. "Other clinical trials are looking at combining different subtypes of influenza (A and B) to develop a broadly protective vaccine or, in some cases, even a universal flu vaccine, thus avoiding the risk of not having selected the right strain for the next flu season. It could help adoption of this vaccine and facilitate its production, while also reducing the frequency of the booster injections," says Nestola. "Of course, the industry still needs more data to assess the feasibility of mRNA in terms of immune response and whether re-optimization of LNP formulations is required for influenza. Nevertheless, mRNA vaccines have proven their superiority in terms of manufacturing speed (it takes around 24 hours to manufacture a batch of mRNA, compared to 2–3 weeks for a cell-cultured-based process). These aspects taken together bring a potentially strong competitive advantage for mRNA. Time will tell if the immune response against other disease targets will be as good as what we saw for COVID-19 or if we need a toolbox to work with different disease targets."

For Payne, the benefit of mRNA lies in its ability to reduce the critical clock speed: "mRNA makes it much faster to design and manufacture the vaccine. At Arcturus, we are finding that next generation mRNA, such as self-amplifying mRNA, may offer even more benefits too – such as lower doses that are much more efficient from a manufacturing perspective because one manufacturing run generates so many more doses."

In this special feature, we speak with companies to find out how they are innovating in influenza – from making monoclonal antibodies, to mRNA – and beyond.

HITTING A MOVING TARGET

By Holge Hannemann, Director of Research, The Native Antigen Company

Influenza viruses A and B are a major public health concern, mainly affecting the pharynx, trachea, and sometimes the lungs of millions of people worldwide each year, with symptoms that range from mild to life-threatening. Alongside seasonal outbreaks (which tend to prevail over the winter months) there is also the looming threat of pandemic influenza strains, which have the potential to bring healthcare systems to a standstill because most people have little or no immunity. The most effective preventative measure against flu is vaccination. Here, I'll explore the challenges associated with flu vaccine development – and the emerging technologies hoping to tackle them.

THE CURRENT VACCINE LANDSCAPE

Most influenza vaccines elicit antibodies against the major viral surface proteins, hemagglutinin (HA) and neuraminidase (NA). This poses a challenge for vaccine formulation because evolutionary changes in these proteins enable the virus to evade the adaptive immune response through a combination of phenomena known as antigenic drift and shift (1), as shown in Figure 1. Antigenic drift occurs when influenza viruses continuously undergo changes to their HA and NA surface proteins through mutation. These changes accumulate over time, transforming the viruses and allowing them to escape host recognition without hindering their ability to gain entry to cells. Antigen shift, on the other hand, is much rarer and is defined by abrupt changes to HA and NA through genome reassortment by influenza A with other influenza subtypes that are co-infecting the same host cell, made possible by the segmented nature of the influenza virus genome. These drastic changes allow influenza viruses to catch our immune systems completely off-guard and rapidly spread through populations, leading to pandemics. The 1918 Spanish Flu and 1968/1969 flu pandemic are two notable historical examples of this. As a result, vaccine formulations must be regularly updated to keep up with emerging forms of the flu viruses.

Standard flu vaccines are formed from inactivated and live-attenuated viruses produced using chicken eggs – every year, vaccine producers consume millions of eggs in this process. Although this is the current leading strategy, it is a highly complex and time-consuming process, typically taking 6–8 months to produce sufficient quantities. Because of the long timescales involved, the WHO meets twice yearly to predict and select the vaccine components for the upcoming influenza seasons in the Northern and Southern Hemispheres. These predictions inform the entire vaccine development chain – from the reagents used for research and development through to selecting formulations and manufacturing the vaccines themselves. Unfortunately, despite these efforts, vaccine efficacy is usually under 60 percent – and can even drop as low as 10 percent (2). Uncertainties in strain prediction can result in vaccines that significantly differ from the strain circulating for that season (3).

Because vaccines play such a vital role in preventing serious flu outbreaks, the challenges in their development and production pose a real threat to human health. This risk is exacerbated during pandemics, as we saw in the devastating 2009 Swine Flu outbreak – during which a delayed vaccine roll-out is thought to have caused thousands of additional deaths (4). Consequently, there has been a significant push within the industry for more sustainable and effective alternatives.

One avenue currently being explored is a universal flu vaccine. A successful universal vaccine would ideally eliminate the need for seasonal re-formulation by providing robust, long-lasting protection against multiple subtypes of flu and emerging strains, as opposed to just a select few. A popular target for universal vaccines is HA's stalk domain, which plays a fundamental role in membrane fusion. Unlike the head of the HA protein, the stalk typically remains unchanged and the elicited antibodies tend to ward off a variety of other strains (5). A number of candidates are in development, with various approaches being taken.

ALL EYES AHEAD, ALL EYES ON THE BALL…

Although they are now famous thanks to Moderna and Pfizer-BioNTech, mRNA vaccines had been in development as alternatives to live attenuated/inactivated virus/recombinant protein vaccines for a while before the SARS-CoV-2 pandemic hit. The technology works by delivering mRNA to cells that subsequently express HA proteins, which the body can then produce antibodies against.

We have seen how successful the platform can be, allowing researchers to quickly swap mRNA encoding for different antigens. This technology holds great promise for influenza because it provides a means to rapidly change the vaccine target without repeated approval procedures, and thus use highly modular technology and manufacturing to hedge bets against and rapidly respond to emerging and potential pandemic strains. Other benefits of mRNA vaccines include a shorter manufacturing period than traditional egg-based methods, and greater potential efficacy. Combining this technology with

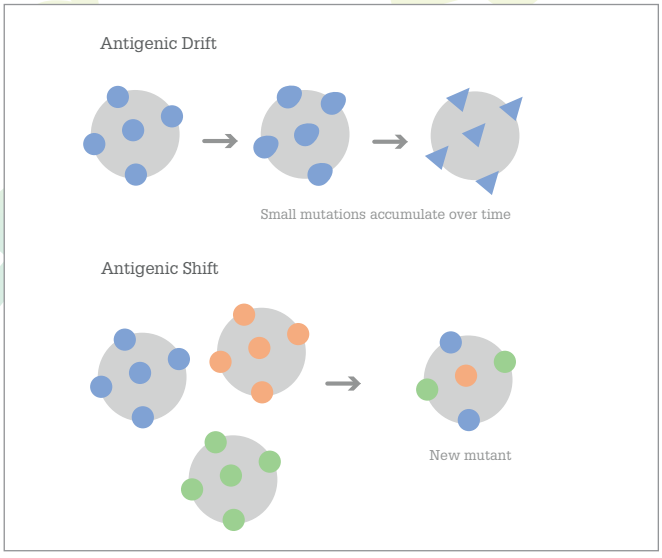


Figure 1. Antigenic drift is the gradual accumulation of smaller mutations, whereas antigenic shift is a sudden, drastic change.

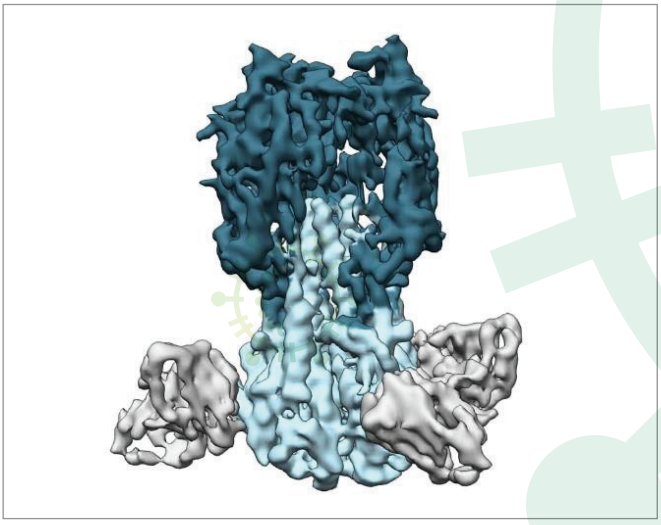


Figure 2. Traditional seasonal flu vaccines target the "head" of the HA protein, whereas universal vaccines trigger antibodies (partially shown in gray) that bind to the stalk (light blue) (7).

universal vaccine approaches could be key to overcoming the challenges of season flu and erasing the threat of pandemics.

A team of researchers at the University of Pennsylvania is using mRNA technology to test a universal vaccine that contains HA proteins from 20 different flu lineages (6). Studies in mice and ferrets have shown promising results in reducing signs of illness and protecting against death, even when exposed to strains not included in the vaccine.

Though these new technologies present exciting developments and possibilities for the future, it is also important to focus on improving existing vaccines and create solutions that can be immediately implemented. Next-generation adjuvants could provide answers by enhancing and modulating the immune response. Adjuvants are substances that boost immune response through various mechanisms – including the creation of antigen depots, the activation of the innate immune response, the recruitment of immune cells, and improvements in antigen uptake. Currently there are only six licensed adjuvants available in combination with flu vaccine: Alum, MF59, AS03, AF03, virosomes, and heat labile enterotoxin. Thus, there is much space yet to explore. The discovery and design of novel adjuvants could be particularly helpful for inducing robust antibody responses in high-risk populations, such as the elderly or those with pre-existing conditions.

Ultimately, emerging technologies offer a great deal of promise in tackling flu – and the COVID-19 pandemic has already demonstrated our ability to rapidly deploy some of these with real success. To continue along this trajectory, reagent companies, like my own, must continue to support vaccine developers and manufacturers by providing the very latest high-quality products to facilitate efficient R&D. We do this by regularly updating our supplies according to the latest WHO predictions, ensuring researchers have access to relevant recombinant proteins as quickly as possible. Such cooperation and communication will enable mankind to continue to strengthen existing and new approaches for flu vaccine development. Through improved strain prediction and disease surveillance, we will be able to build a comprehensive defense against the moving target that is influenza.

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A DAY IN EGG CITY: SEVEN THINGS I LEARNED ON A VISIT TO BRITAIN'S LARGEST FLU VACCINE FACTORY

By Angus Stewart

On a recent rainy day in Liverpool, UK, I visited a factory owned by one of the world's largest flu vaccine producers: Seqirus (a company headquartered in Australia). Astute readers of The Medicine Maker might well remember our 2021 coverage of Seqirus, Don't Shoot the Messenger, where we interviewed Seqirus' Head of R&D, Russel Basser. Truly devoted readers may also recall Stephanie's previous conversation with Basser from 2020, Preparing for the Next Pandemic. During my visit, I did not meet Basser (who is actually based in Australia), but I did meet and speak with Nige Hilton, the company's VP of Manufacturing and Head of its Liverpool site. During the course of the day, I learned a great deal about influenza and the moves mankind makes to fight it through vaccinations. Below, you'll find my seven choice Flu Facts: please inoculate yourself with them, and walk away that little bit the wiser.

1. AS CANDIDATE CITIES FOR VACCINE PRODUCTION GO, LIVERPOOL IS HARD TO BEAT

When I asked Hilton if operating in England's northwest conferred any particular advantages to Seqirus, he noted (after a caveat that he is from the opposite side of England's north) that workers in Liverpool – or at least in Seqirus' factory – have a humble, self-effacing, yet extremely capable quality. "Nothing seems to be too much trouble for them," he said. "They're really committed and, even in the face of difficulties, they just get on with the job."

After I pushed Hilton on whether Liverpool offers anything special beyond the character of its people, he affirmed that the city's academic institutions – from the Liverpool and John Moores universities to the Pandemic Institute (a natural ally!) – provide a huge boost to Seqirus and its incoming workforce, whom Hilton confirmed are largely hired in and around Liverpool. To borrow a Scouse phrase: "That's boss."

2. THE SEQIRUS SITE PROBABLY "EATS" MORE CHICKEN EGGS PER DAY THAN LIVERPOOL'S RESIDENTS

Depending on how one counts, the population of Liverpool sits at around half a million, which puts the Liverpudlian headcount slightly under the Seqirus UK's daily egg count (approximately 575,000 eggs). Normally, it's thinking about Earth's place in the universe and the number of stars around it that sets me down a road of existential questioning, but I will freely admit that trying to mentally grasp Seqirus' egg count also leaves me rather dizzy.

Most of you will know why a vaccine facility needs eggs, but please allow me the time to help those scratching their eggs – I mean, heads. Put (very simply), the vast majority of influenza viruses destined for the world's flu shots are grown inside chicken eggs. The technique has a pedigree reaching back to work on growing viruses conducted in 1931 by one Ernest William Goodpasture, which eventually translated into inactivated, egg-incubated flu vaccines rolled out by the US military during World War II.

As an editor rarely afraid to pose a potentially silly question, I asked Hilton how Seqirus likes their eggs. Does size matter? The kindly Site Head assured me that size does not matter, but pointed out that other quality factors do. At the 21 hatcheries that supply the Seqirus site, every measure possible is taken to reduce the hens' bioburden (exposure to pathogens).

3. CRACKS ARE SHOWING IN THE EGG'S THRONE

By 2032, Seqirus – and influenza vaccine manufacturing at large – may have moved on from its close relationship with the chicken egg. The storm of the COVID-19 pandemic triggered the first ever rollouts of mRNA vaccines, and now many in the industry believe these entirely chicken-free vaccines could be the future.

Even Seqirus is riding the mRNA train, having developed its own self-amplifying mRNA technology, which Hilton says could work well as a means to incorporate multiple flu strains into a single vaccine. When quizzed a little harder, Hilton elaborated that, in the next couple of decades, he would like to see Seqirus putting out both adjuvant and mRNA products on a more global scale, but was also willing to confess that much of what lies ahead depends on certain unknowns, such as the emergence, safety, and adoption of these and other new technologies.

4. SEQIRUS' PARENT COMPANY WAS BORN AMID GLOBAL TURMOIL

Though the reign of the egg-based vaccine may end long before its hundredth birthday, Seqirus' parent company, CSL, is in no such danger. In fact, it is already 106 years old. The "C" in CSL (Commonwealth Serum Laboratories) gives a hint as to its origins. Midway through World War I, the Australian

government was facing an unreliable supply of medicines from overseas, so to help the country become more self-sufficient the government set up CSL as a state enterprise for the production of a range of vaccines – as well as antitoxins to deal with the nasty poisons of the continent's infamous array of deadly insectile, reptilian, and ocean-borne creatures.

In 1919, CSL went through a trial by fire as Spanish flu arrived in Australia, despite a coordinated quarantine the previous year. Four in ten of the country's population caught the virus, and 15,000 died. Arguably the next-most pivotal moment in CSL's history came in the mid-nineties, when the Australian government privatized the company. For the purposes of this article, the next major event came in 2014, when CSL bought and absorbed Novartis' flu vaccine business, rebranding it to Seqirus in 2015.

Today, Seqirus does retain something of a link with the state sector – but in more than one state. During my visit, the various Seqirus authority figures in attendance were not at all shy in stressing how much they collaborate and comply with the national governments whose winter flu jab campaigns they supply. In fact, Seqirus also works with numerous national governments on pandemic preparedness too – 30 of them, to be precise.

5. SEQIRUS HAS A NEAR-MONOPOLY ON SUPPLY FOR THE UK SEASONAL ADULT FLU VACCINE

If you have received a winter flu jab in Britain, then you are very likely a part of this story. In the 2021/22 flu season, Seqirus supplied 9 out of 10 of vaccines in the seasonal adult flu vaccine program. That translated to 20.3 million jabs in England, 2.8 million in Scotland, 0.8 million in Northern Ireland, and 0.6 million in Wales (roughly proportional to the population in each country apart from Wales, which has a smaller relative share).

Despite the major slice of the pie that Seqirus commands, a number of other suppliers' vaccines ran alongside them in the market in the 2021/22 season, and will largely remain there for the coming 2023 season. These include one egg-grown and one cell-grown quadrivalent vaccine from Sanofi, and a children's nasal spray from AstraZeneca. Seqirus' egg-grown virus is the only vaccine on the list specialized for the elderly, but the company has another cell-grown vaccine for ages two and up. For hardcore vegans, I would recommend the latter.

6. OUR COVID-19 LOCKDOWNS AND RESTRICTIONS DECIMATED FLU INFECTIONS

You may not be surprised to know that during the period of massive global lockdown that much of mankind undertook to alleviate the COVID-19 pandemic, infection figures for influenza dropped massively. Seqirus has a keen eye on this because it appears to have knocked the "usual" cycle of winter and summer transmissions off its axis. The (relative) resumption of normality in early 2022 saw reemergence of the flu, but at lower rates than before and in a spike-dip-spike pattern from January through July. On my visit, several people were keen to stress that what comes next is something of an unknown, but that a post-lockdown surge could be on the cards.

The big technical question regarding such a surge was: "Which strain or combination of strains will governments need to vaccinate people against?"

Now that we know, the data generated may prove useful when (not if) another pandemic triggers further major quarantine events…

7. DATA FROM THE SOUTHERN HEMISPHERE CAN HELP INSTITUTIONS IN THE NORTHERN HEMISPHERE BRACE FOR WAVES OF WINTER FLU, AND VICE VERSA

Earlier in this listicle, we established the Australian origins of CSL. For flu, a little transhemispherity (or should it be "transhemispherism"?) goes a long way. Flu strikes in winter and recedes in summer, and on either side of the equator those seasons are inverse. Watching a current winter flu in one hemisphere can help you to predict what the next winter flu will do in the other. Surging or shrinking numbers in nations of the southern hemisphere – in this case Australia – can be correlated with social factors also likely to take effect in the north, and vice versa.

Across 2022, analysis by Seqirus in Australia reported a rise in flu infections that was both unusually high and unusually early. They have suggested that this could have been linked to two factors: the return of the nation's children to school after the summer holidays, and the peak of the Omicron wave. The flu spike also triggered a "twindemic," in which the Australian healthcare system almost buckled under the combined weight of the Omicron wave and a flu spike. Ambulances stopped picking up new patients, and the system began to bleed staff as worsening working conditions pushed nurses and others to leave in search of better paid and more peaceful career paths.

So what can the northern hemisphere learn from what happened in Australia? First and foremost, the events may serve as a generalizable demonstration of what happens in a wealthy country when flu returns after a period of relative absence. One Seqirus expert advised that the best approach may be to "hope for the best, and prepare for the worst," and to that I would add: Be thankful not only for modern pharmaceutical science, but also for modern mass-scale egg logistics.

TEACHING OLD VACCINES NEW TRICKS

Featuring Joseph Payne, President, Co-Founder, and CEO of Arcturus Therapeutics

In 2013, Joseph Payne and Pad Chivukula were feeling entrepreneurial and decided to start a new company with just $15,000. Arcturus Therapeutics was born. Since then, they have raised over $500 million from investment capital and grown the company to around 175 employees.

The company's focus has always been on the safe and effective delivery of high-efficacy, therapeutic mRNA – which meant the company was well placed when all eyes turned to mRNA during the COVID-19 pandemic. When the SARS-CoV-2 virus first started as an epidemic in the southeast Pacific, the Singapore government reached out to Arcturus to learn more about the company's self-amplifying mRNA (samRNA) technology. At the time, Payne says no one had any idea how much COVID-19 would transform the world, and how vital mRNA technology would be in saving it…

What happened next? Find out in our interview with Payne.

TELL US MORE ABOUT ARCTURUS' COLLABORATIONS…

We received funding from Singapore's Economic Development Board for our early research efforts to identify and evaluate samRNA vaccine candidates. Vietnam then stepped forward and we received funding from the Vingroup – the number one corporation in the country – for a large-stage clinical trial. Our technology was proven safe and effective – and we saw 95 percent efficacy in protecting people from hospitalization and death due to the SARS-CoV-2 delta variant. We now believe that we have a comprehensive data set that showcases how samRNA vaccine technology could be a next-generation platform for boosters against COVID-19, and how the same samRNA technology may be employed in the fight against other epidemics, including influenza.

In 2022, we announced a partnership with CSL – one of the top flu vaccine companies in the world – to develop and commercialize next generation mRNA vaccines using our STARR and LUNAR technologies for SARS-CoV-2, influenza, pandemic preparedness, and other respiratory infections. Arcturus received an upfront payment of $200 million from CSL with additional development and commercial milestone payments, and 40 percent profit sharing for the COVID vaccine franchise. CSL Seqirus, a division of CSL, has built an extraordinarily successful flu vaccine enterprise. We look forward to helping CSL Seqirus advance the next generation mRNA (samRNA) technology through their flu vaccine pipeline.

And there's still more! We are also collaborating with a Japanese company called Meiji, with whom we are running the first phase III trial ever to directly compare samRNA technology to conventional mRNA technology in a non-inferiority comparison trial involving 780 participants. This potentially approvable trial could allow us to file for registration and commercialization in Japan.

WHY ARE YOU SO EXCITED ABOUT THE POTENTIAL OF SAMRNA?

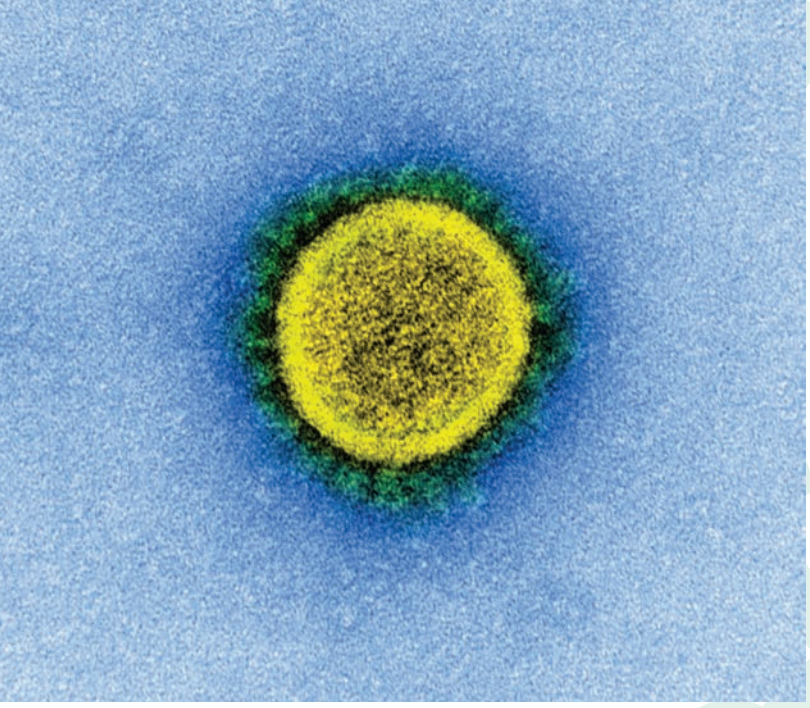
samRNA vaccines are a much lower dose technology; you are infecting less mRNA, using fewer excipients, and so on. We have been evaluating a dose level of 5 µg – in contrast to the 30, 50, or even 100 µg doses seen in conventional mRNA vaccines. samRNA vaccines could also be more effective. Conventional mRNA vaccines make the antigen for 1 to 2 days, giving the body a limited window in which to "see" the antigen and initiate an immune response. With samRNA, vaccines express antigen for one to two weeks, allowing for a much stronger and longer-lasting immune response. We have also found in our early phase II trials that antibodies generated from our vaccine are protective against alpha, beta, gamma, delta, and omicron variants of SARS-CoV-2.

Finally – and crucially – our platform produces a lyophilized vaccine, which eliminates the supply challenges of dealing with cold chain, a significant headache for existing vaccines which must be transported and stored in controlled refrigerated or frozen conditions. This is hard enough for vaccines being moved across the country, but a nightmare for international shipments. Lyophilized vaccines, by contrast, can be shipped and stored at ambient temperature, making stockpiling and distribution a far simpler and less error-prone process.

WILL VACCINES MADE USING SAMRNA STILL NEED REGULAR UPDATES?

So far, it seems as if the samRNA vaccine platform may generate antigens that provide a broader immune response, which may mean that the vaccines do not need to be updated as frequently as with conventional mRNA – but we still need to collect more data. That said, I think it is inevitable, no matter the technology, that vaccines will need to be updated on a periodic basis because viruses like influenza and SARS-CoV-2 can rapidly mutate. It's only a matter of time before the mutation is substantial enough that you need to update the technology to capture and protect against the new variant.

Credit: National Institute of Allergy and Infectious Diseases, NIH



IS PANDEMIC FLU STILL A CONCERN?

The WHO warns all governments globally about what could be the next outbreak or pandemic – and number one on that list is pandemic flu. If avian flu or swine flu mutate to spread to humans then it could be very, very serious – far worse than what we have seen with COVID-19. Consequently, there is now renewed emphasis in preparing and stockpiling for another pandemic.

Arcturus has also been active in the area of pandemic preparedness, working with BARDA (Biomedical Advanced Research and Development Authority), the US government agency charged with the development of advanced medical countermeasures to respond to 21st century health security risks. We have funding to develop and clinically evaluate a pandemic flu vaccine with the potential to be stockpiled, using our samRNA technology. Doses should be small, which means you can stockpile a large amount of doses in a small footprint that can be deployed quickly if there is an outbreak. COVID-19 has taught us that pandemics are real and that we need to be prepared – unless we want another multi-trillion dollar mistake and global disaster on our hands.

WHAT OTHER LESSONS MUST WE TAKE AWAY FROM THE COVID-19 PANDEMIC?

Scientists warned of a SARS-CoV pandemic back in 2015 – and at that time, a SARS-based vaccine was not developed. This was a lesson for us all and we must take warnings from virus surveillance committees more seriously and be more prepared in the future. If we have stockpiles and plans in place, we can squash these outbreaks in their infancy, before they get out of control and become a global pandemic, with all the associated loss of life and disruption to global infrastructure we saw in 2020. If the COVID-19 pandemic taught us anything, there is a high price to pay for lack of preparation.

WHAT IS THE FUTURE POTENTIAL OF MRNA?

Vaccines are only scratching the surface of how disruptive this technology can be in the pharmaceutical industry. It has the potential for use in cancer vaccines and other therapeutics. The lion's share of currently approved drugs deal with the downstream symptoms of the disease. Whether it is pain or inflammation, swelling, hardening of arteries, or cancers – all of these stem from a genetic precursor. DNA is rarely perfect – and dysfunctional or missing elements can lead to disease. The existing therapies work to suppress symptoms, mRNA can go right to the source. If we can go into the body and replace what's missing or broken in a targeted fashion at the cellular level, then we can potentially normalize the life of a person living with a debilitating disease.

Aside from our work on COVID-19 and influenza, we have a lot of exciting mRNA therapeutics in our pipeline. For example, we are working on a liver disease called ornithine transcarbamylase deficiency (OTCD), where patients have a missing or altered protein function that disrupts the urea cycle. The disease causes ammonia levels to rise in the blood, which can cross the blood-brain barrier and damage neurological tissue. OTCD can cause seizures, coma, and death in untreated patients, there is currently no cure for OTCD. mRNA encased in lipid nanoparticles, injected intravenously, could help restore normal urea function. Our candidate treatment for OTCD is LUNAR-OTC and it is currently in phase II trials. If successful, it would use Arcturus' mRNA technology to replace the missing liver enzyme inside the patient's own liver cells, restoring liver function and allowing patients to live a normal life. We expect more data later in 2023.

We are also exploring the potential of inhaled therapeutics for the lungs. There are many lung diseases caused by missing proteins, such as cystic fibrosis, which is one area we think mRNA could help. Our candidate here, ARCT-032, received approval at the end of January 2023 to proceed into a first-in-human study in New Zealand. Our preclinical data have shown robust expression and functional restoration of the cystic fibrosis transmembrane gene in human bronchial epithelial cells from donors with cystic fibrosis, and we are very excited to see the first results from trials in human patients. If successful, this therapy could revolutionize the treatment of cystic fibrosis, allowing patients, most of whom are children, to lead a normal life instead of living with a daily routine of physiotherapy and medications simply to manage their symptoms.

The scope and breadth of human disease that is addressable with therapeutic mRNA is vast – and with everything Arcturus has in development, 2023 is going to be a very exciting year.

For the Birds

Early reporting, rapid action, biosecurity, culling, surveillance. These remain the most effective protective measures against avian flu, according to UK Government guidelines (1). But if we break these down, they seem quite far from a scientific approach. "Early reporting" sounds like the media should take the lead, "biosecurity" is a code word for quarantine and isolation; "culling" (mass murder in a human context) sounds very much like a last resort; and "surveillance" reminds us to go back to step one. It all just feels a bit more dystopian than scientific. Why the reluctance to bring in proven vaccines?

For one, the practice is currently restricted by government legislation (2) and permissible only by zoos with a current license, which seems logical when we consider the rationale opposing mass vaccination of game and poultry. The manpower it would take to vaccinate each individual chicken, duck, goose, and so on would be astronomical, while placing farmers, vets, and bird handlers at increased risk. The firebreak strategy implemented by the UK may seem a little conventional considering the number of years (and pandemics) that have passed since it was legislated, but how does this tactic compare with other countries?

The European Commission works alongside the WHO, the UN FAO, and the World Organization for Animal Health in the development of its strategy, which doesn't much differ from the UK's – a legacy of its now lost EU membership, perhaps. Surveillance, movement restrictions and "the strictest biosecurity measures" have been in place since 2003, but the bloc seems to have placed more emphasis on education and communication: "Disease awareness amongst farmers and co-operation by all persons in the poultry sector must ensure that the strictest biosecurity measures are applied to prevent the introduction of the HPAI virus in the establishments and the (further) spread of the disease" (3).

In November, the US was close to reporting a record number of avian influenza cases (4), according to the CDC, in which we gain an insight into the country's own containment strategy. "Since early 2022, more than 49 million birds in 46 states have either died as a result of bird flu virus infection or have been culled (killed) due to exposure to infected birds." Echoing the culling strategies already observed in the UK and EU, the US also advises maintaining a safe distance from wildfowl or infected poultry, and the use of PPE and good hygiene strategies – including a change of clothes when necessary – if it is necessary for humans to make contact with infected birds.

Aside from these, the US strategy also stretches to social media-based communication and vaccinations in the event of a human contracted avian influenza. As far as we know, avian influenza is not a threat to human health – not yet at least. Devastating for the birds, certainly, but for humans, the ethos remains one of ongoing surveillance and monitoring with the back-up plan of vaccination in case of avian-to-human and human-to-human transmission.

Creditt: Lorrie Graham/AusAID

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Hugo Fry

FLU SEASON: MARCH OF THE MABS

As the world continues to take on the post-COVID flu epidemic, we ask RQ Bio CEO Hugo Fry what part monoclonal antibodies play in new flu treatments

HOW IS THE 2022/2023 FLU SEASON FOLLOWING DIFFERENT BEHAVIORAL PATTERNS – AND WHY?

The flu season is hitting its peak while there is still a significant amount of COVID-19 circulating, which creates an excessive burden on healthcare systems, leading to delays in diagnosis and treatment across a broad spectrum of medical conditions. By addressing and preventing flu, it's possible to deliver both a medical benefit and a broad public health impact.

HAS THE PANDEMIC AFFECTED HOW RQ BIO DEVELOPS MABS FOR INFLUENZA?

Yes. We are using the pandemic as proof of concept for the value of mAbs in protecting vulnerable populations against a viral disease that drifts and mutates. We are applying these proof points to our development of antibodies to protect vulnerable populations against influenza.

Though vaccines remain the cornerstone of active immunization, vulnerable populations that cannot build an immune response with vaccination can benefit from protection from other interventions, such as mAbs. We have seen this with COVID-19, and we believe that the same passive immunization approach will be valid for influenza. And that's why we initiated a flu antibody discovery program.

WHAT'S INVOLVED IN THE DISCOVERY PROCESS?

Finding a potent and broadly neutralizing antibody is extremely difficult because they are very rare. There are good reasons for this. It is in the virus' interest to constantly mutate to evade our immune system. On the other hand, our immune systems favor potency, wherein we can fight today's battles well, over breadth, wherein we can worry about tomorrow's battle another day. These two factors explain why we can get infected multiple times by COVID-19 or flu.

The beauty of our immune system is its potential to make millions of different antibodies. We look for extremely rare antibodies in human blood that have both breadth and potency against specific viruses. Millions of antibodies are scanned from multiple donors and we apply specific techniques for sieving these antibodies, including high throughput cell sorting and sequencing coupled with computational biology. Another way to increase our chances of finding them is to generate the antibodies by immunizing special strains of mice (which make human antibodies). Designing immunization strategies to increase the likelihood of finding these special antibodies is challenging as the immune system will naturally select for potency over breadth. Our team has specific expertise in both the immunization and the selection methods for identifying these needles in the immune haystack.

WHAT ROLE HAS MISINFORMATION AND/OR MISTRUST PLAYED IN THE GROWING PRESSURE ON HEALTHCARE SYSTEMS DURING FLU SEASON?

On balance, I would say there has probably been improved trust in the biopharma industry following the scientific advances made during the pandemic. The industry came together – with other stakeholders – to produce effective vaccines, antibodies, and treatments in a timeframe that was previously unimaginable. I think many people realize it contributed hugely to saving lives and has been widely appreciated.

That said, misinformation has long been the enemy of protection through immunization – going all the way back to the first vaccines. The role of education will continue to be a major contributor to public health. Improved education leads to better policy and improved vaccination rates across the eligible populations, which helps relieve pressure on healthcare systems.

WILL WE EVER SEE THE END OF FLU?

We are unlikely to see the end of the flu virus. But, as medical science continues to develop, we can hope that the impact of flu on public health – and society more broadly – will be less severe with the advent of new innovative preventions and treatments.

BROAD STROKES

Universal flu vaccines have been a holy grail for many years – and Centivax believes it could be onto a breakthrough with its broad spectrum vaccine approach to influenza and other pathogens

"A post-pathogen humanity." This is what biotech company Centivax is working towards by developing broad-spectrum vaccines for a variety of infectious diseases – including influenza.

The genesis of Centivax dates back to around 2012, when Jacob Glanville was building a previous company called Distributed Bio, which was using computational immunology to identify new therapeutic antibodies to target specific protein sites. However, the tools the company was developing also provided better insights into immune systems – such as the induction of autoimmunity and the failure of vaccines for quickly mutating viruses.

"At that point, I realized that I had invented a vaccine technology and I worked to develop it further," says Glanville. "It was the beginning of a golden age of biotechnology. We had access to high-throughput genomic sequencers that we could point at the immune system to look at tens of millions of antibodies and T cell receptors. High-throughput synthesis technologies also allowed us to use DNA synthesis to build antibody libraries of thousands of human immune systems, which could be interrogated in vitro. This work gave rise to some new ideas around the conserved sites that exist in otherwise mutating viruses, and why our immune systems so often miss these sites. If we can get the immune system to focus exactly on these conserved sites, we can create universal vaccines."

Glanville spent years developing the technology in Guatemala – where he grew up and where he is also an affiliate professor at the University of San Carlos. Distributed Bio was performing well as a business and profits allowed the technology to develop, until it was eventually noticed by the Bill & Melinda Gates Foundation.

"We were selected for a Millennium Grand Challenge: End the Pandemic Threat award," says Glanville. "A lot of science that gets funded is iterative rather than disruptive, and there will always be reviewers who don't agree with a new idea. The funding from the Bill & Melinda Gates Foundation was a huge breakthrough and allowed us to conduct studies in the US with key collaborators. But let's not fool ourselves – this is only the beginning and we have a lot of work to do!"

On December 31, 2020, the Distributed Bio services business was sold to Charles River laboratories – on the condition that Glanville could spin out the universal vaccine technology. "Many of the Centivax co-founders have known each other since 2008, so we've pulled a dream team together to execute this," says Glanville.

The company's portfolio includes "universal" vaccines and antibodies against rapidly mutating viruses – as well as bacteria. However, Glanville explains that "universal" is not quite the correct term. "The term 'universal' when applied to vaccines is a buzzword; a more accurate description is 'broad-spectrum.' Unlike current flu vaccines and current COVID-19 vaccines, our vaccine should produce antibody responses against non-mutating sites and therefore will have a broad spectrum effect against the majority of viruses that could occur in the future. But biology is complex and eventually it will defeat you. Universal implies that the vaccine won't ever require modification, but I don't have the data right now to say if that will be the case or not. It may be that the vaccines still need modifying, but it should be far less frequent than current approaches – vaccines updated perhaps a few times per century, instead of the current practice of updating the vaccines every single year."

HITTING THE RIGHT TARGET

The idea of a universal – or broad-spectrum – flu vaccine has been discussed amongst researchers for years. Despite numerous early-stage projects, there has been no true breakthrough. According to Nick Bayless, Chief Technology Officer of Centivax, influenza belongs to a club of viruses that have the same challenging hallmark: rapid mutation. "This isn't true of all viruses, but HIV, influenza, and the coronavirus mutate very rapidly as a survival strategy to avoid the immune response," says Bayless. "There are many different mechanisms involved in how each virus does this, but essentially they change the parts on the virus that are recognized by antibodies, which means that the immune system is unable to prevent the next infection after the virus has mutated."

But even viruses that mutate rapidly are bound by certain goal-based constraints; for example, the influenza virus has to enter human lung cells and the HIV virus must enter human T cells at a certain efficiency. The viruses attack their target cell by precisely docking onto a receptor on that cell, much like a rocket must precisely dock with the airlock on the ISS to deliver astronauts. Ultimately, this creates bottlenecks in viral evolution; the virus cannot mutate the "airlock" or it is unable to dock and is therefore no longer infectious. This conserved docking site creates a conserved and vulnerable patch that antibodies can attack and prevent all viruses from docking.

"However, these rare, conserved epitopes are outnumbered by all the epitopes on the rest of the viral surface that can mutate

Three of Centivax's founders: Jacob Glanville, and Stephanie Wisner, and Nicholas Bayless,

– and a typical antibody response will go after the parts of the virus that is changing year to year," says Bayless. "Our technology targets these areas because we know these viruses cannot infect cells without them."

Glanville adds, "The first time that someone described a broadly neutralizing antibody hitting a conserved site on flu was back in 1993. More papers were published in the 2000s and this started a race for a 'universal' vaccine, but everyone was flying blind because the tools for interrogating the immune system weren't good enough; it's only in the past ten years or so that we've really seen a revolution in high-throughput sequencing and DNA synthesis technologies."

In other words, scientists were trying to fix an engine when they couldn't lift the hood. Glanville also points out that there has been a lot of attention directed at why our immune system don't target the conserved sites of viruses over the last decade. "Computational biology allowed me to understand more about what is going wrong – and how we can fix it."

DILUTING FOR STRENGTH

Centivax's technology is state of the art, but Glanville has a simple way to describe it. The company takes 10 representative versions of influenza vaccine, dating all the way back to 1918. "These strains are all very different to one another, but there are some conserved sites – as Nick explained – that have not changed. We take these strains, mix them together, and dilute the mixture. There is not enough of any of the ten individual strains to produce an immune response – but there is a large enough dose of the shared site, because all ten components share that exact site."

So far, Centivax has tested its approach in animals – and they, as well as laboratories at the University of Georgia and Auburn University, have observed it providing protection for up to twelve years of future evolution of the viruses. And critically, the approach was able to neutralize future variants of the virus that didn't exist when the study began. "Now, we're preparing to run in vivo studies for validation of our delivery of our vaccine using LNP mRNAs, and then we can enter manufacturing," says David Tsao, Chief Operating Officer and co-founder. "Initially, we were planning to commence manufacturing earlier this year, but we've decided to hold fire because there is the possibility that our approach will be compatible with the mRNA lipid nanoparticle systems that have been used in COVID-19 vaccines."

"The advantage for us is that those systems are much faster to manufacture, are less expensive, and have a built-in ability to stimulate the immune system," explains Glanville. "And they have been de-risked significantly over the last two years. There are advantages and disadvantages to every delivery platform, but we're excited by the mRNA studies we have ongoing. If we go the mRNA route, it could speed things up getting our vaccine into clinical studies."

Centivax's most advanced program is its flu vaccine, but the company is also working on a broad-spectrum coronavirus vaccine and is starting to apply its technology to HIV (both vaccines are currently in animal testing). Another area the company is interested in is a side effect of some mRNA COVID-19 vaccines: myocarditis – and whether it is possible to engineer delivery systems to avoid the side effect. "We should always make the delivered medicine as safe as possible," says Glanville.

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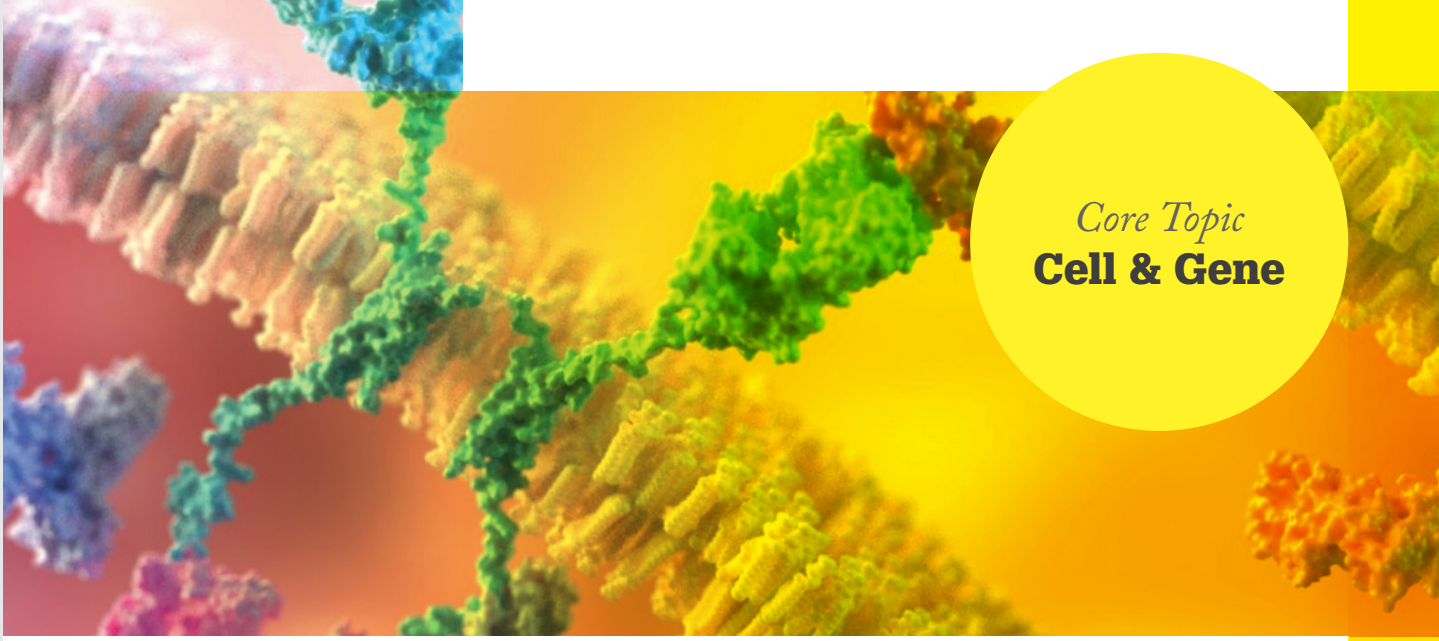

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Core Topic
Cell & Gene

Reaching the brain. How can we get gene therapies across the blood-brain barrier? Researchers at the University of Wisconsin-Madison working on gene therapies for the brain have used nano capsules of silica to achieve gene editing using CRISPR technology in the brains of mice. The surfaces of the silica nanocapsules were modified with glucose and an amino acid fragment derived from the rabies virus to allow them to penetrate the blood-brain barrier. The approach was used to edit the amyloid precursor protein gene, which is thought to be related to Alzheimer's disease.

Pompe disease trial restarts. In June 2022, the FDA put a clinical hold on the phase I/II trial of Astellas's gene therapy candidate for late-onset Pompe disease after a case of nerve damage – peripheral sensory neuropathy. At the time, the FDA stated that Astellas did not have sufficient information to assess the risks to subjects. Now, the clinical hold has been lifted and dosing has resumed. The gene therapy is AT845 and uses the AAV8 vector to deliver a functional copy of the GAA gene. Astellas recently presented preliminary safety and efficacy data from the trial.

Residues begone. When a cancer removed by surgery comes back, microscopic residual cells are often to blame. It's a thorny problem, but a recent study at the University of Pennsylvania may have found a way to solve it. UPenn scientists delivered CAR T cells into the cancer surgery wounds of mice via a gel, and found that in nearly all cases, mice that would have otherwise died from cancer recurrence survived. The university's Carl June weighed in, giving a verbal thumbs up, and added that the gel method could potentially be expanded to include delivery of cell therapies and anticancer agents.

Adverse events. California's Graphite Bio has paused the phase I/II CEDAR trial of Nula-cel (its gene-edited autologous hematopoietic stem cell therapy for sickle cell disease) after the first ever patient dosed experienced a serious side effect. Since treatment in August, the patient has suffered from prolonged low blood cell counts (pancytopenia) that require ongoing transfusion and growth factor support. Nula-cel has been singled out as the culprit. During the pause, Graphite will look into risk factors and mitigation strategies, including potential modifications to the manufacturing process. The company had planned to file an IND by mid-2024 and is now working to extend its cash position until at least 2026.

IN OTHER NEWS

New understanding of graft-versus-host disease published by researchers (F Sacirbegovic et al; DOI: 10.1016/j.immuni.2023.01.003) shows GVHD is maintained by donor T cells that seed tissues soon after transplant

Eurofins CellTx opens 15,000 square foot laboratory in Tucson at the University of Arizona Tech Park to support growth of testing services for cell and gene therapies, cord blood, and bone marrow

TTP launches new spin-out company Cellular Origins to focus on scalable and cost-effective manufacture of cell and gene therapies

England's cost watchdog NICE finally approves Yescarta for routine use on the country's National Health Service

Researchers at the National University of Singapore look to bring cell therapy to dogs by using stem cell precision engineering technology to treat canines with cancer

Cell and Gene: Generating the Next Generation

Thousands of cell and gene therapy trials are underway; assuming at least some success what can the field do to avoid a seemingly inevitable rush on supporting products and services?

If you've been following cell and gene therapy news (perhaps by subscribing to our Cell and Gene newsletter), you will know that the field's pricing problem remains very much intact. Many are calling for more automation as a remedy, but what does that look like in practice? And besides automation, what other forms of crucial and auxiliary support could help grease the wheel for cell and gene therapy (CGT)? To glean a little insight, we spoke to a veteran on the frontlines: Thermo Fisher Scientific's Vice President and General manager of Cell and Gene Therapy, Betty Woo.


Betty Woo

What is Thermo Fisher Scientific's role in cell and gene operations…

We have a history of serving cell and gene therapy developers through a broad offering of tools, substances, and services. More recently, we have also begun selling fit-for-purpose products for the clinical and commercial manufacturing of cell and gene therapies. These include closed, automated, and modular systems that can be integrated into flexible workflows, and GMP-grade media, growth factors, and reagents that are chemically defined and/or animal-origin free. In addition, our technology was used in the isolation and activation of patients' T cells in the first commercially available CAR T therapy.

The business I lead actually spans many individual businesses across Thermo Fisher, integrating our products into workflows and collaborating with our customers to develop processes that address industry challenges, such as scalability, inefficiency, and cost. Time is of the essence in this rapidly moving field; the faster we can demonstrate clinical utility, the faster these technologies and products can help patients.

What is the current state of demand?

Cell and gene therapies are still relatively new. Though just over 20 cell and gene therapy products are currently approved by the FDA, there are more than 2,000 ongoing clinical trials for cell and gene therapies. This has created a major demand for supporting products and services to bring these critical therapies to market, faster.

What kind of scaling-up and automation for CGT has Thermo been able to implement?

Manufacturers tend to cite scaling, standardization, industrialization, and automation as the field's top challenges. The first generation of CGT manufacturing workflows required hours of manual manipulation of cells, media, and consumables – all through highly skilled labor. The industry has now begun applying automation to minimize this need for manual intervention, thus reducing the potential for human error and standardizing the manufacturing

process – and, ultimately, resulting in a second generation of more reproducible and robust workflows.

What are the main obstacles to adoption of "second generation" workflows?

There are three considerations that stay foremost in the company's mind.

The first is an awareness of the very conservative manufacturing environment, in which chemistry, manufacturing, and controls practices and regulatory requirements are necessary to ensure that quality and safety standards are met. The "cost" of these standards is that new process paradigms and disruptive technologies have to clear a high hurdle to achieve acceptance and adoption across the industry.

The second is the lack of global harmonization in the regulatory requirements for cell and gene therapies, including the basic definitions and scope of what is included in these drug classes – not to mention quality standards.

The third is the variability and accessibility of raw materials. As the field matures, this consideration will become increasingly critical. Clearer regulatory guidance in defining GMP-grade starting materials and the presence of animal-derived components is key to reducing variability in manufacturing.

How far are we from an end-to-end integrated workflow?

In the case of the more complex scenario for autologous cell therapies, the process starts with cell collection from the patient and comes full circle to the delivery of a modified and expanded cell therapy back to the same patient. The whole process is complex, and so here the goal of end-to-end integrated workflow remains "aspirational," rather than immediately achievable.

Homing in on the cell therapy manufacturing process itself, we are working toward an end-to-end automated process that starts with cell isolation and activation, progresses to cell engineering, expansion, and finally to formulation/fill/finish and cryopreservation.

And how will we get there?

We saw during the pandemic that the fastest way to support innovation is through collaboration. By aligning stakeholders to work together with the patient in mind, we can optimize workflows and increase scalability to expedite the delivery of therapies to more

A Patient Story in the UK

Libmeldy gene therapy is used for the first time in the UK outside of a clinical trial

Given that this publication is designed for professionals working in development and manufacture, we often focus on the inner workings of the industry – from drug discovery methods to business partnerships and approvals. But sometimes it's important to feature the patients – just a quick reminder (if ever one was needed) of why you do what you do. In the UK, a patient story being widely reported in the media emphasizes just how ground-breaking gene therapies can be.

Cell and gene therapies have been slow to come to the UK market and have been heavily scrutinized by the UK's drug spending watchdog, NICE. Take Orchard Therapeutics' Libmeldy as an example. The gene therapy was approved by the EMA in 2020 to treat the fatal genetic disorder metachromatic leukodystrophy (MLD). In the UK, the drug was then rejected for use by the country's drug cost watchdog because it was priced at £2.8 million (around $3 million). After negotiations, the UK finally agreed to use the therapy in its healthcare system in February 2022 – and the first child received treatment in the summer.

The child (Teddi Shaw) was 19 months old at the time and now, six months on, is reportedly healthy, happy, and showing no signs of the disease. However, the story is bittersweet. The child's older sister, Nala, was also diagnosed with MLD, but was not eligible for treatment because she had already developed symptoms of the disease. Her parents are now forced to watch as her condition deteriorates. Life expectancy for MLD is five to eight years.

MLD results in the build up of sulfatides in the brain and other parts of the body, with patients eventually losing the ability to walk, talk, and interact.

We don't yet know the full long-term effects of Libmeldy, but children who received the therapy in a clinical trial are reportedly doing well, including a boy, Joe Elson, who received the therapy in 2014. In a similar case to Teddi, Joe was diagnosed alongside his older sister – when she began showing symptoms.

Gene therapies certainly save lives, but there is work to be done. With respect to MLD, children need to be diagnosed much earlier. And although the benefits of such a therapy absolutely justify the high price tag, it doesn't change the fact that healthcare systems across the world are cash-starved. The industry must find a way to bring down costs to prevent any further delays in patients receiving treatment.

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Core Topic
Bioprocessing

Outlook for Humira biosimilars. A white paper from Goodroot expects incoming Humira biosimilars to the US market to have a tough start, with Humira rebates likely making it difficult for biosimilars to get onto formularies for 2023. In fact, the report goes as far as saying that Humira's preferred placement on formularies has historically been "untouchable." Cost savings caused by the entry of Humira biosimilars are expected to be "minimal" initially, but could capture a market share of around 25 percent by 2026. A number of factors are expected to play a role in influencing which biosimilars become the most preferred, including concentration (high concentration likely to be preferred), pen-injector availability, manufacturer reputation, net costs, and supply chain security.

mAbs for Alzheimer's. Lecanemab continues to see regulatory successes; the drug has been approved by the FDA (and greeted with cautious optimism amongst stakeholders), is under review at the EMA, and has gained priority review status in Japan. But another anti-amyloid therapy on the block – Eli Lilly's donanemab – has fallen short of the goalposts. The therapy has received a complete response letter from the FDA, with the agency requesting that Lilly supply "data from at least 100 patients who received a minimum of 12 months of continued treatment on donanemab." Both drugs have similar targets but different trial designs.

Learning about MAM. Scientists at NIBRT have published a research paper in Nature Protocols (S Millán-Martín, C Jakes, S Carillo et al; DOI: 10.1038/s41596-022-00785-5) that offers guidance on the implementation and deployment of the multi-attribute method (MAM) for biotherapeutic characterization. MAM allows CQAs to be monitored at the amino acid level simultaneously and directly, including identity testing based on primary sequence verification, and detection and quantitation of post-translational modifications and impurities. It is considered a more streamlined and productive workflow for biopharmaceutical analysis than conventional chromatographic and electrophoretic assays.

Tackling obesity. A phase IIb study conducted by Versanis Bio is assessing the safety and efficacy of first-in-class mAb bimagrumab in combination with semaglutide for the treatment of obesity. Versanis Bio claims that the mAb is the only candidate in clinical development for obesity that drives fat loss while also increasing muscle mass. More than 20 studies with bimagrumab have already been conducted, including a 48-week phase II study in type 2 diabetes patients with obesity. The mAb "produced a placebo-adjusted approximate 22% fat mass loss coupled with 4.5% lean mass gain, despite minimal change in caloric intake."

IN OTHER NEWS

CEPI partners with Tiba Biotech and provides $2 million to evaluate RNA vaccine platform technology, RNABL

Fujifilm Irvine Scientific launches BalanCD HEK293 viral feed to boost adeno-associated viral vector production for gene therapy and viral vector based vaccines

BioNTech forms partnership with UK government focusing on clinical trials for personalized mRNA cancer immunotherapies; aims to reach 10,000 patients by end of 2030

Catalent completes 12,000 sq ft plasmid DNA manufacturing facility in Belgium; can support customers with requirements for high yields at 50 and 300-L fermentation scale

San Jacinto College and McCord Development (both in Texas) sign memorandum of understanding with NIBRT to provide biotechnology training programs

A Tale of Two Inhibitors

Two drugs, two different destinies. Does their story prove that business practice makes the difference?

Bristol Myers Squibb's PD-1 inhibitor drug, Opdivo, is known to many – but did you know that the drug's origins have one foot in Japan? Around the year 2000, the drug originated from intellectual property related to the PD-1 gene, created by Japanese company Ono Pharmaceutical Industries, in collaboration with scientists at Kyoto University. Subsequently, the US company Medarex initiated full-scale drug development, using its humanized antibody development technology. Ono received approval from Japanese regulatory authorities to use nivolumab to treat unresectable melanoma in July 2014, which was the first regulatory approval of a PD-1 inhibitor anywhere in the world.

Winners and losers

The Japanese origin of Opdivo is of particular importance to Kota Kodama (Associate Professor, Ritsumeikan University), the lead author of a new paper published in Drug Discovery Today that examines the "victory" of Merck Sharp & Dohme's PD-1 inhibitor Keytruda over Opdivo. The two drugs are very similar and were both approved in 2014 but, despite an initial regulatory and commercial lead, Keytruda's sales have eclipsed Opdivo's since 2018.

"I wanted to know what caused the first immune checkpoint inhibitor that can be said to have originated in Japan to lose out to a latecomer," Kodama explains. "In the long term, I wanted to know what kind of development management would lead to the success of follower drugs."

So how can a drug win in science but lose in business? Like any good thorny conundrum, the problem offers the scholar and the investigator numerous angles of approach.

Defeat and its lessons

Kodama's angle of analysis was life cycle management (LCM), which he defines as "management that maximizes drug sales at an early stage and keeps them there as long as possible." Is this where Opdivo's owners went wrong? Merck, the paper concludes, took better care of Keytruda by spending heavily to boost its pipeline in moves such as the acquisition of biotech companies with particularly useful strengths. The paper also suggests that better focus on collaborations that bring PD-1 inhibitor drugs into clinical trials as part of a combination therapy would improve their commercial development, as would securing a greater number of indication approvals.

"The goal of pharmaceuticals is not just to get them to the bedside, but to have them used by more people and in more situations to restore their health."

Kodama saw his intuitions and hypothesis confirmed in these conclusions, telling us he thinks the paper's results and recommendations were "predictable." However, he notes that some questions are still up in the air and that the external environment and even luck are important determinants of success.

But there are other factors that companies such as Ono and BMS can hope to control a little more easily than raw luck. First, there is mindset. Kodama is firm on this. "The goal of pharmaceuticals is not just to get them to the bedside, but to have them used by more people and in more situations to restore their health. Drug development researchers, including me, tend to forget this, and I believe that more emphasis should be placed on the importance of development management and its education."

Twin drugs, twin disciplines

In the Japanese context, there is also room for improvement – and walls to be knocked down. Kodama explains, "In Japan, the barriers between the natural sciences, social sciences, and humanities tend to be very large. There is little communication between the disciplines. Consequently, the country produces very few people with the combination of scientific and managerial expertise needed to carry out highly successful development management for drugs. We need to create an environment that educates and develops professionals and experts with multiple disciplines under their belts – say, natural science and social science."

To the question of whether a study of one drug versus another is enough to draw major conclusions, Kodama insists that a retrospective comparison between two companies and their drugs is sufficient for a reasonable level of generalization. He feels quite comfortable in asserting, for example, that active and effective alliances related to the drug right before it is launched will lead to better LCM. However, every paper has its limits, and every study needs a sequel.

"To predict the future," Kodama muses, "further research is needed."

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Core Topic

Small Molecule Manufacture

Yes we cannabinoid. Catalent and Ethicann Pharmaceuticals have announced a development and license agreement whereby Ethicann will apply Catalent's Zydis orally disintegrating tablet (ODT) technology to its clinical drug pipeline. Catalent will develop Ethicann's CBD and THC pharmaceutical products in clinical trials focussing on multiple sclerosis spasticity, chemotherapy-induced nausea and vomiting, chronic pain for cancer, and epilepsy. Ethicann's EPI-002 candidate formulated with Zydis ODT dissolves in seconds and is rapidly absorbed through the lingual and sublingual mucosa into the blood, bypassing the liver. Ethicann anticipates performing a human bioequivalence study as early as Q4 2023.

Pharma photocopier. Researchers from the Department of Pharmaceutics and Biopharmaceutics, Philipps-Universität Marburg, Germany, are looking to improve the bioactivity of the antibiotic Norfloxacin using paper-based pills. The "smartFilm" technology involves loading the active compounds onto paper. APIs are dissolved in an appropriate solvent and applied to the cellulose-based paper matrix, dried, and harbored in the pores of the paper. No proof-of-concept study has yet been undertaken, but the researchers claim that the paper can be manually transferred into tablet forms.

Modification over management. Cyclarity Therapeutics is seeking to address age-related diseases such as atherosclerosis by repairing the accumulation of toxic biomolecules in cells and removing the cellular waste that causes immune cell dysfunction, inflammation, and plaque accumulation. Conventional methods focus on slowing plaque accumulation and reducing the risk of cardiovascular events. Cyclarity is instead adopting an engineering approach to remove damage and repair cells with a disease-modifying drug, UDP-003. Cyclarity believes the drug can bring around a radically reduced cost burden of atherosclerosis treatment options, as well as address the steadily rising incidence of annual CVD mortality.

Taking on the mantle. The FDA has approved Eli Lilly's Jaypirca (pirtobrutinib) for adults with relapsed or refractory mantle cell lymphoma (MCL). The drug uses a novel binding mechanism and is the first non-covalent BTK inhibitor to be approved by the agency. Patients must have endured at least two lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor, as Jaypirca works by reestablishing BTK inhibition and extending the benefit of targeting the BTK pathway. Accelerated approval was granted based on response rate from the phase I/II BRUIN trial, but verification and description of clinical benefits from a confirmatory trial will be sought so the drug can obtain continued approval.

IN OTHER NEWS

Researchers in India publish review article on the benefits of plant-derived biopolysaccharides as pharmaceutical excipients for formulations such as gels, tablets, nanoparticles, and more (doi.org/10.1016/j.ijbiomac.2023.123454)

RMIT scientists create new antibiotic that can be re-engineered to avoid resistance. Priscilicidin's small amino acid building blocks can be modified to address different types of antimicrobial resistance (https://doi.org/10.3389/fchem.2022.1009468)

Potentially improved SEDDS-based tablets with better dissolution profiles and bioavailability than conventional simvastatin tablets prepared by researchers in Pakistan using regular excipients and machinery (https://doi.org/10.2147/DDDT.S377686)

The Microbiome Miner

Water is the giver of life, but could it be a giver of untold medicines too? Biosortia CEO Ross Youngs believes so

"Nature loves to hide" – a maxim attributed to Heraclitus (arguably Greece's strangest philosopher and a man adored by modern mystics), but do those four words have any bearing on the world of nature as studied by 21st century scientists? For Biosortia founder Ross Youngs, the answer is a resounding, "yes." Nature is full of secrets – and many are locked away in the microbiome. But now, Youngs argues that we have the means to more fully unlock the microbiome and apply the resulting knowledge to new medicines.

How does algae connect with drug discovery?

The most important small molecules on the planet are found in microbes, but less than one percent of the microbes on the planet can be grown in a culture. From this less-than-one percent, mankind has derived half of the drugs that sit on shelves today – be it directly, indirectly, or through inspiration. Virtually all of today's research is focused on indirect access. Some readers may remember the days of combinatorial chemistry – and they'll remember that it failed pretty miserably.

Biosortia's technology has the potential to break through this deadlock by grabbing microorganisms on a massive scale from where they live in nature, without the need to culture anything. In the context of lab benchtop work, 100 milliliters would be considered a large sample size. Biosortia starts with sample sizes 200 million times larger than that. Our approach is to open up direct access to the most important hidden chemistry on the planet.

Why focus on nature's microbiome rather than the human microbiome?

It's true that there are tens of thousands of unknown small molecules in our bodies. Take a look at the human metabolome database and you'll see that fewer than 140 of the microbial small molecules in our blood have ever been identified. So, you may rightly ask – why does the natural microbiome matter? Well, believe it or not, the water of your nearest lake overlaps with your metabolic pathways and gut microbiome's genes by more than 73 percent. So that water is as about as valid a source as you are – and I'm sure you'll agree that extracting water at scale is preferable to extracting anything from you at scale!

What's your ideal source – river, pond, lake, or swamp?

The beauty of the natural world is that it is as diverse as we humans are. You might think that two lakes in Alabama, sitting side by side and used for exactly the same thing, would have identical or at least very similar microbiomes… But you'd be wrong. Upon testing, every aquatic environment shows up as unique. Temperature, pressure, sunlight, nutrients, pH, and oxygen content – all these variables shape the nature of the microbiome.

Few people realize that, for the last 4.2 billion years, microbiomes have dominated the Earth. Right now, the weight of all living microbes outweighs that of all other living organisms, if we exclude woody biomass.

In other words, we are in such early days that there could be 100 companies like ours mining the microbiome, and we would all be discovering new small molecules that are relevant to the signaling in our cells. We could be at the North Pole or the ocean floor, and we would still find microbiomes. There is no real need to be picky!

That said, I would point to the tropical and subtropical environments of our country's southeast as especially interesting cases. There is a lot of water with a lot of diversity in salt and nutrient content, aerobic and anaerobic respiration, photosynthesis… The kind of variables that could keep a company like mine busy for a lifetime.

How do you find and then "mine" water?

We use a lot of collaborators – many of them from universities – to tell us about appropriate aquatic environments. From these sites, we are specifically looking for places that have not been extensively studied. When you can easily discern peaks of unknown molecules in your sample, you know there is a good chance that the microbiome in question may be of interest. The Biosortia Microbiomics approach is to start with a minimum of 100,000 grams of the dry-weight, high-quality microbiome and separate the desired molecules using extractions and fractionations. The goal is to amplify the hidden chemistry so it can be read by analytical equipment (LC/MS) at higher quantities than two parts per billion. Once we have found an optimal site, we scale up the harvest to large samples of around 20 liters. On these samples, we carry out an initial genomic analysis and then move on to what we call "scouting," which uses equipment that can easily process 10,000 liters in one day, allowing us to collect enough biomass to explore a living, active microbiome. Why genomic and not metabolomic? Because genomics, metabolic pathways, and gene clusters provide valuable relationship information. Metabolomics is also used to understand the actual molecules present, and direct analysis and indirect genomics lead to a greater understanding. If the larger sample also shows promise, we escalate once more to our full-scale unit, which can process over 20 million liters of the source – enough to capture the entire microbiome.

If that figure scares you, then let me put you at ease. The kind of harvest we typically carry out sits at around 20 million liters, which is equivalent to eight Olympic swimming pools. Though that may seem like a lot of water, when stacked against the full volume of a bay or a lake, eight Olympic swimming pools of water adds up to not much at all. I can also assure you that we work with and gain approval from the relevant state, local, and federal authorities who manage these water sources. After we finish conducting our prospecting, the microbiome will completely recover in less than one day.

We typically collect 1 million grams of the dry-weight microbiome from 20 million liters of the aquatic microbiome source, and that biomass is stored at a maximum of -20°C. Based on our initial analysis of the small molecules and references to data sets, we arrive at a greater understanding of the chemical novelty. Typically we find tens of thousands of addressable (i.e. obtainable) novel small molecules.

How exactly do you find those new and interesting small molecules?

Deep analytical data is collected on the fractions of the small molecules, including LC-MS/MS and other computational or analytical data.

This 2D data provides insight for projecting opportunities when coupled with training sets on known small molecules and activities for AI prioritization. For example, we may use a training set for antiviral activities, and artificial intelligence analysis may then help us to uncover new antiviral opportunities from the unknown small molecules of the microbiome. Just as the human microbiome holds a wealth of novelty in inflammation and neuromodulation, we can see that the microbiome has the potential to be the greatest untapped source for antiviral activity, once we take into consideration the wealth of microbes and viruses (or phages) that outnumber the microbes 10 to 1.

Additionally, we're developing several scanning strategies (some in-house and some with partners) to assess the potential of the many new small molecules we retrieve in every single harvest. Artificial intelligence (AI) is quite interesting in this context. When using machine learning for drug discovery, AI can work with either real or predicted data. Predicted data is easier to come by but when you are working with computations upon computations, errors can amplify. In short, using real data produces better output; we can see this in the application of machine learning on approved drugs to discover new ones.

In our approach, we can apply the power of AI to tens of thousands of unknown and untested small molecules to pinpoint potential opportunities, helping us prioritize our next steps for testing those molecules. Antivirals, immunology, and oncology are great places to start because the existing scientific literature has shown that the gut microbiome is key in modulating the immune systems of humans.

And what will you do with the promising molecules?

Our goal is to execute at full scale and be able to provide these molecules to partners; for example, private biotechs, pharmaceutical companies, or academic institutions. To enable those handovers, we plan to build a library of molecules, understand them, prioritize them, and curate them. We want to focus on the molecules as intellectual property, and let experts outside our company handle the medicine-making procedures. Though it's true that you cannot patent a natural molecule, you can patent its activity. Discover that activity and the patent can be yours.

What impact do you hope this work will have in the future?

I believe our work is a revolution in the making. I would say that ten years after we have begun executing at scale, you will hardly find an academic institution or an industrial company involved in life sciences that isn't directly mining microbiomes for what I'm not afraid to describe as "the hidden secrets of life".

In fact, I'll go further and say that this technique is so productive that in ten years, the vast majority of life science products will derive from it. If one percent of the world's microbes have given us half of our existing medicines, think about what the full 100 percent could do. Nature has had billions of years to create the cell signaling chemistry that runs through biology, and this shift could open it all up to us.

NextGen

R&D pipeline
New technology
Future trends

Cell and Ex Vivo Gene Therapies: A Manufacturing Odyssey

Demand for cell and gene therapies is increasing, but are current manufacturing approaches up to the task? Technology companies are on the case and new solutions are emerging. Here, we explore the key considerations when developing ex vivo gene therapy and cell therapy processes for commercial manufacturing.

By George Todorov, Cell & Gene Therapy Process Expert at IPS – Integrated Project Services LLC

In recent years, ex vivo gene therapies have stirred hope for a curative treatment for B cell malignancies and, in the future, solid tumors. Somatic cell therapies have also been shown to be effective against metastatic prostate cancer and in hematopoietic or immunologic reconstitution therapies.

CAR-T, CAR-NK, and T cell receptor (TCR)-T cell therapies are generated by administering recombinant genetic material that alters the properties of living cells. Genetic alteration of the cells is performed outside the body before the cells are delivered to the patient, so these therapies are classified as ex vivo gene therapies. In contrast, somatic cell therapies are human cells transplanted to repair damaged tissue or cells, and include modalities such as hematopoietic or mesenchymal stem cells and cellular immunotherapies.

Both ex vivo gene therapies and somatic cell therapies have seen clinical success and commercial licensure. Cell immunotherapy products such as CreaVax RCC and Immuncell-LC have been licensed in South Korea since 2007. Dating back to the early 2010s, Dendreon's Provenge was among the first somatic cell therapies to receive FDA and EMA approval. However, CAR-T cell therapies have taken longer to reach commercialization. Yescarta and Kymriah secured FDA approval in 2018, paving the way for others, such as Tecartus, Breyanzi, and Abecma.

Ex vivo gene therapies and somatic cell therapies come in two flavors: autologous and allogeneic. Autologous cell and ex vivo gene therapies are often considered a safer approach than allogeneic equivalents because there is no risk of graft versus host disease. CAR-T therapies were originally established as autologous products with the need to "scale out" the manufacturing processes to serve a growing market. However, scaling out presents major manufacturing and economic challenges at the commercial level, which has led developers to heavily invest in allogeneic modalities. Allogeneic products can enable scale up of manufacturing processes and "off-the-shelf" solutions that will treat large patient populations, while also lowering cost and reducing manufacturing and supply chain complexity.

Planning for the future

With the number of cell and ex vivo gene therapy products entering the clinic growing exponentially, we must, as an industry, look ahead and plan accordingly so that we can deliver these revolutionary medicines to large patient populations safely and efficiently. Regardless of the specific modality – and the autologous or allogeneic format – cell therapy processes are not standardized and there is significant room for evolution. A number of serious questions remain unanswered:

How does one efficiently scale out or scale up autologous and allogeneic manufacturing processes to meet growing demand?

How can an inherently open manual process be converted to a closed and semi or fully automated process?

What does the evolving regulatory landscape for cell and ex vivo gene therapies push us to anticipate when designing a manufacturing process?

What do we, as an industry, need to consider when planning to manufacture

multiple patient lots and/or multiple cell therapy products under the same roof?

How can the cost of manufacturing be lowered to make these life-saving therapies more accessible?

The autologous way

The autologous cell therapy industry has rapidly embraced single-use technology and closed processing for GMP manufacturing, but currently available formats for cell processing present logistical challenges for high capacity multi-product and/or multi-client manufacturing. Equipment developers have in recent years provided two contrasting approaches for closed processing of autologous therapies:

i. Modular, single-use equipment that addresses the need of individual processing steps or stages (apheresis, cell isolation, engineering, expansion, and harvest/formulation).
ii. End-to-end equipment with single-use consumables that encapsulates the entire process, following apheresis, in a single instrument.

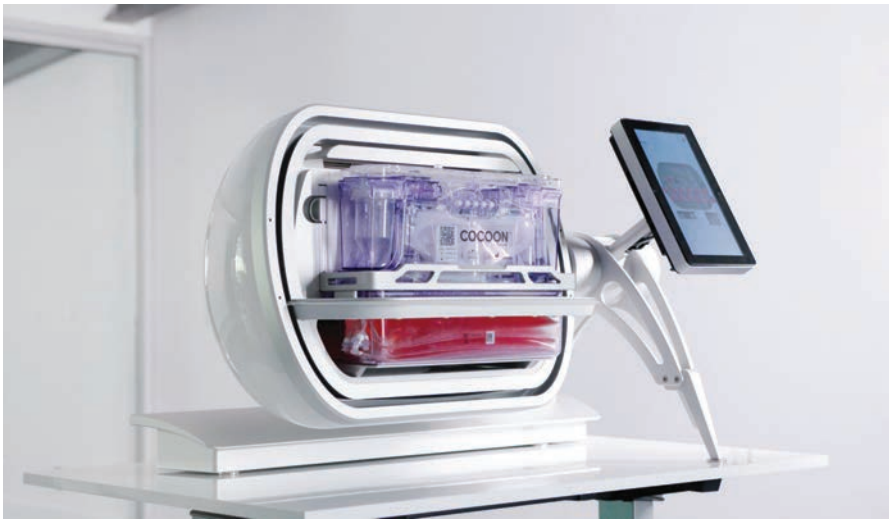
The hype around CAR-T cell therapies has spurred bioprocess equipment manufacturers into a competitive race to offer modular instrumentation. The result? Plenty of choice for manufacturers. Terumo, Thermo Fisher Scientific, Cytiva, Fresenius Kabi, and others now offer a variety of instruments with parallel functionality, leaving the end-user with several possible configurations and a wide range of processing strategies. Similarly, there are now multiple vendors offering end-to-end solutions in a single system, including Miltenyi, Lonza, Draper, and Cellares. Developers must carefully consider the tradeoffs between housing the process in one system versus multiple specialized instruments.

End-to-end instruments have a small footprint but this approach ties up the whole instrument for 1-2 weeks while a single batch is produced. Separate instruments, on the other hand, can have higher utilization while accommodating multiple batch processing in the same space. This is possible because not all manufacturing steps require the same amount of time to complete. For many processes, the cell expansion operation requires the bulk of the manufacturing time. With separate instruments, facility footprint and capital can be dedicated to the cell expansion equipment to minimize the bottleneck, while other equipment can be limited in quantity and readily shared between batches.

Unfortunately, there is no one right answer; the best configuration is largely dependent on the drug manufacturer's capacity requirements, process duration, available cleanroom space, and manufacturing model (in-house versus CDMO). Benchtop end-to-end solutions may be a great approach for small clinical programs or quick manufacturing processes and, as throughput demands increase and plans are made for commercial scale-out, it is common to see clients adopt a hybrid approach. For example, clients may perform T cell enrichment, activation, and transduction in a Miltenyi CliniMACS Prodigy, expansion steps in wave reactors, and harvest/wash/formulation in a Cytiva Sefia or similar instrument. In this example, a low number of Prodigy and Sefia instruments are used for the front and tail ends of the process, while an army of wave reactors takes care of parallel batch expansions to increase throughput and allow for parallel processing in the same space. If hybrid and modular processing approaches for autologous manufacturing retain their utility as the industry matures, there will be a significant opportunity to weave in automation. It is also possible to envision robotic systems shuttling and manipulating batches of cells between modular instruments, which would increase efficiency and throughput, while lowering operating costs.

Adding complexity to the maze of end-to-end instrumentation, Lonza offers the Cocoon, which encapsulates the entire process in a single-use cassette format (see Figure 1). It delivers similar capability to the CliniMACS Prodigy, in a much smaller footprint, and can integrate with the Lonza Nucleofector to enable electroporation. Lonza is also developing a Cocoon Tree format that enables a compact scale-out approach by packing a large number of Cocoon pods in a small space, which could be a highly effective solution for high-capacity manufacturing plants or CDMO facilities. When manipulation is required, a motorized system rotates the pods to make them accessible for the operator. Another option, expected to hit the market in 2024, is the Cellares Cell Shuttle – a fully automated end-to-end cell therapy system that uses an industrial robot to move closed cell processing cartridges between unit process operation stations from cell enrichment to formulation. However, the Cell Shuttle does not integrate a fill station, so the user must consider a separate filling solution. The system can execute over 10 workflows simultaneously and, by taking advantage of this format, developers can cue up

Figure 1. Lonza Cocoon (1).



multiple batches staggered behind one another (see Figure 2).

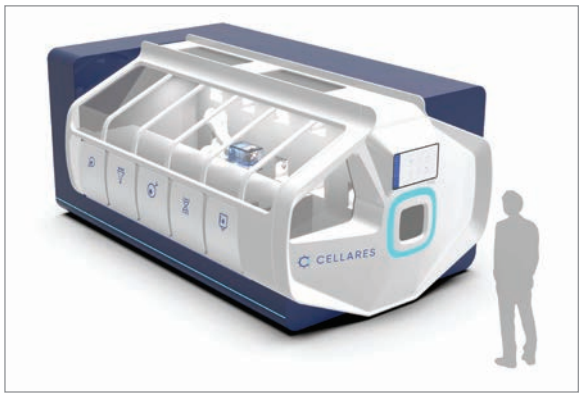
Closed or open?

Today, there is an abundance of closed processing options for autologous ex vivo gene and cell therapies, all with their own pros and cons, but the majority of cell therapy programs begin R&D and process development in academia with open, manual operations in a biological safety cabinet (BSC). It is a tremendous challenge to rapidly transition a BSC process to closed systems – and the cost of single-use equipment is usually prohibitive to academic labs. However, it is critical to industrialize academic processes prior to technology transfer for GMP manufacturing to avoid program delays, improve product safety, and simplify regulatory review. To help address this gap, developers and academic institutions are investing in collaboration centers that will help bring GMP manufacturing infrastructure and equipment to cell therapy programs developed in academia.

But what about leaving the process open? Sure, this may be an unpopular idea these days, but avoiding a complete overhaul of the original BSC process can accelerate development timelines – if developers have a good approach to maintaining an aseptic environment. In recent years, isolator manufacturers have heavily invested in the ex vivo gene and cell therapy industry to bring these novel processes into well-established Grade A aseptic processing environments. Companies such as ProSys, Comecer, SKAN, Harro Hofliger, OPTIMA, and their partners have delivered innovative isolator configurations that offer end-to-end processing for manual or partially automated manufacturing, and manual or fully automated filling systems for fully closed vials or cryo-bags.

Adopting isolator technology comes with significant upfront investment, which often scares away small companies. However, this knee-jerk aversion to the cost fails to consider the long-term advantages of isolators in commercial manufacturing. Adding to the advantages of operating in an aseptic environment, housing the process in an isolator can realize considerable cost savings during the facility build and operation because this approach enables manufacturing in a Grade C room rather than Grade B. An isolator system may cost several million dollars, but the annual disposable gowning cost for a single technician operating in a Grade B cleanroom can run to ~$30,000, excluding Grade B operator training, qualification, and re-qualification. One year of operation

Figure 2. Cellares Cell Shuttle (2).



can quickly surpass the cost of an isolator when operating a cell therapy facility of ten or more Grade B suites, to a point where the isolator truly pays for itself in such settings.

Furthermore, modular isolator configurations allow for process and equipment flexibility because they can be configured and strung together with bespoke modules that can evolve with the process (see Figure 3 as an example). This type of configuration allows for independent decontamination of each module, enabling multi-product manufacturing in the same space. Operating the isolator in an assembly line fashion maximizes system utilization as batches progress through processing modules. Though several isolator providers offer similar functionality, some are taking leaps in engineering automation solutions to enable high throughput processing. For example, CO.DON AG is manufacturing their Spherox product in an automated facility featuring Comecer's FLEXYCULT mobile incubation system for docking incubators that are shuttled between isolators and a CNC area using a robotic handler running in a central spine corridor (figure 4). Innovations such as modular processing isolators and the FLEXYCULT enable processing of a large number of autologous batches in a small number of isolators, and allow us to dispel the notion that legacy manual processes cannot be scaled out.

It is important to note that all of the approaches to multi-product manufacturing described above are closely monitored by regulators, and are acceptable provided adequate measures are taken to prevent cross-contamination and mix-up of materials. Chain of identity is paramount

Figure 3. Modular isolator configuration, courtesy of SKAN (3)

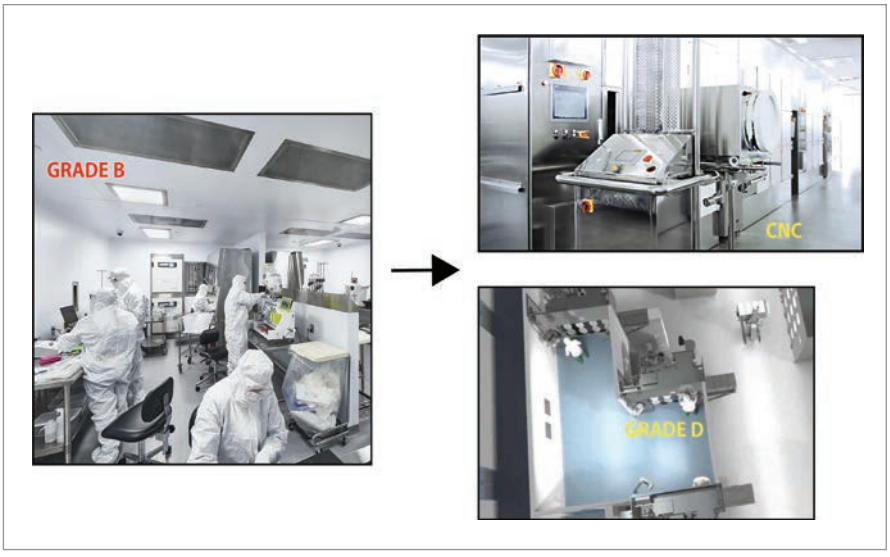


Figure 4. FLEXYCULT system with incubator handler in CNC, courtesy of COMECER (4). Grade B image supplied by IPS.

for autologous products; hence, sponsor companies must have established and validated systems to track the donor material and engineered cells throughout each step of the process, subsequent sampling, storage, and shipment. It is only acceptable to house more than one batch or product in the same space if using closed and contained systems. Regardless of whether one uses closed single-use equipment or isolators, the EU Guide on GMP specific to ATMPs calls for 100 percent air exhaustion when using more than one viral vector for engineering ex vivo gene therapies in the same room.

Allogeneic considerations

While autologous therapies are often considered the faster route to securing life-saving treatment, such a generalization fails to consider the supplier's total batch capacity and the point at which batch production can actually begin. Allogeneic therapeutics can circumvent the nightmare scenario of a patient dying before an autologous batch production is complete or even initiated by providing an off-the-shelf alternative that could potentially help thousands of patients per batch. Autologous and allogeneic ex vivo gene therapies and cell therapies share many process elements, and though the cell expansion and harvest may vastly differ in scale, they have common scientific principles (figure 5). These similarities present some advantages to developers and CDMOs looking to transition from autologous to allogeneic – or wanting to house both modalities under one roof. That said, here are few key differences to bear in mind:

- A healthy donor typically provides the starting material.
- Tissue typing should be carefully matched with receiving patients to avoid host rejection or the need for immunosuppression.
- Isolated immune cells or stem cells are banked prior to initiating the manufacturing process, akin to a master cell bank that is used for biologics manufacturing.
- Allogeneic cell therapies are expanded to a much larger scale.

Regardless of the therapeutic modality (CAR-T, stem cell, cellular immunotherapy), allogeneic processes require scaling up rather than scaling out – taking the early-stage process and increasing the output of product using larger equipment sizes or volumes to generate enough product to treat a larger patient population. However, these therapies are generated with primary human cells that have a finite population doubling, so the feasible culture scale-up cannot currently reach the volumes of biologics. Combining scaling up and scaling out together could be a useful approach to address limited population doubling. For example, scale up to 50 L or 200 L could then be scaled out to multiple 50 L or 200 L reactors. Culture intensification is also highly desirable to maximize the cell density of allogeneic and autologous batches, which is why some developers are using perfusion to increase the output of both modalities.

The scale up challenge

When planning for scale up, care needs to be taken to select a scalable bioreactor platform and to provide adequate space, utility connection sizes, and locations. In many cases, ceiling-based utility panels are used for flexible equipment location and size. In the case of specific workstations or areas, planning for increased equipment size or relocation of equipment should be done ahead of time to ensure that operation can be maintained after the changes are implemented. Culture scale up principles from biologics manufacturing are applicable and transferrable, including maintaining a power-volume ratio or constant oxygen mass transfer coefficient to ensure autologous cells are exposed to similar conditions across bioreactor scales. Human stem cells and primary cells are much more sensitive to shear stress than immortalized cell lines, so alternatives to stir-tank reactors may need to be considered. Besides wave reactor technology, some manufacturers, such as Kuhner and PBS Bio, offer scalable low-shear single-use reactor systems of up to 500 L that can be used for suspension or microcarrier cultures. Harvesting and formulating allogeneic products will require appropriately scaled single-use centrifugation systems

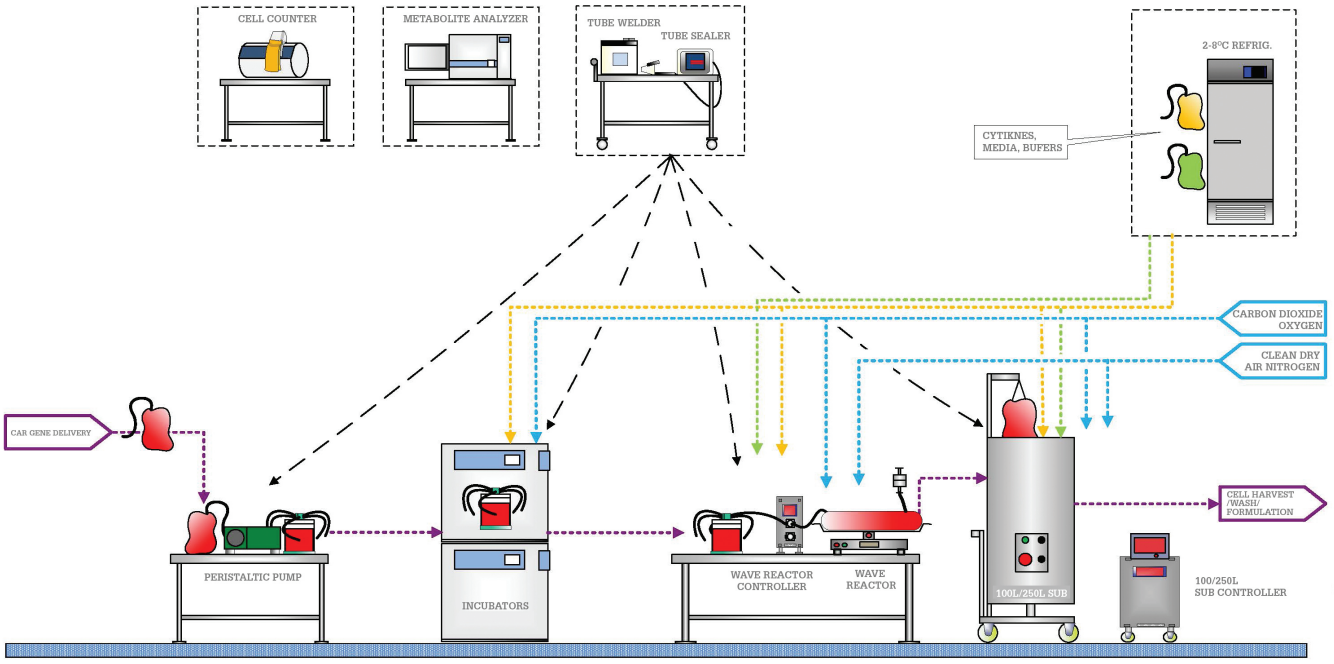


Figure 5. Representative ex-vivo gene therapy cell expansion for allogeneic products.

Figure 6. Crystal L1 robotic vial fill line (A) and Single Use Support ROSS.FILL CGT bag filler (B) (5, 6).

with buffer exchange functionality. The Sartorius kSep platform and the UniFuge line of instruments from Carr Separation Technologies both offer flexibility in scale, excellent recovery and viability.

The final fill, inspection, and labeling steps present a looming challenge to allogeneic processes as they grow in scale. After the point of DMSO (or other cryopreservative) addition, there is a narrow window of 1-2 hours during which the product must be filled, inspected, and labeled so that the cryopreservation cycle can be started in time to avoid damage to the cells. It is therefore imperative to get a head start on studying and designing these final steps to avoid costly complications during a facility design or late stage clinical studies. Automated vial filler providers, such as Aseptic Technologies and Flexicon, offer sophisticated and customizable systems that can be integrated into isolators to maintain an aseptic environment (see Figure 5A). Processes terminating in a bag fill rather than vials can also be automated and scaled. Innovators such as Single Use Support now provide aseptic filling systems that feature a single-use disposable fluid path and can simultaneously fill multiple single-use bags to accommodate a wide range of batch sizes (Figure 6B). Selecting an isolator and/or automated filler are important steps, but they must not be done in a vacuum. Understanding the throughput requirement, batch size and timing of filled vial nests or batches of bags exiting the filling chamber is critical to informing the strategy for labeling and inspection.

Manual inspection is time-consuming and, as batch sizes increase, one must plan for multiple inspection stations, adequate space, and enough personnel. Semi-automated or automated inspection solutions are available from various suppliers, including Korber Pharma, Antares Vision, and Brevetti. This kind of instrumentation was originally designed for large-scale pharmaceutical inspection; however, scaled down versions are now available to serve the cell and gene therapy industry. Analogous to the isolator paradigm discussed above, automated inspection equipment is a costly investment but can decrease processing time, staffing needs, gowning costs, and the required cleanroom footprint. Also, keep in mind the fact that manual or automated visual inspection must satisfy USP 788, 790 and 1790 guidelines, and implementing automated inspection requires lengthy validation studies that must be executed at the manufacturing site.

Last but not least, labeling can be manual or automated, but both the timing and location for this operation must be considered. Labeling is typically done in a

Grade D or CNC environment, but some cell therapy developers consider performing this function in the filling suite to avoid wasting valuable time in moving the product to another area ahead of cryopreservation. Performing labeling in the filling suite raises the concern of introducing particulates in a Grade C environment and one must properly package and sanitize incoming labels, but alternative strategies are now available, such as laser-etching QR codes and product information on the vials prior to the fill or applying pre-printed label sleeves following cryopreservation, to alleviate the fill/finish timing constraint.

The road ahead

Autologous and allogeneic ex vivo gene therapies have significant process overlap, including cell isolation, activation, engineering, initial expansion, formulation, and the need for cold chain. For example, cell isolation, activation, and expansion procedures take advantage of antibody-conjugated paramagnetic beads to capture the correct cell type or mimic interactions that trigger activation and cell expansion. A magnetic field is applied to isolate cells that will be engineered into autologous or allogeneic products, or to remove magnetic beads from the culture after processing. Biodegradable paramagnetic beads are also readily available and developers must weigh the benefits of eliminating the de-beading step against the results obtained with different bead products and the risk of introducing residual impurities.

Engineering ex vivo gene therapies to express a CAR gene is predominantly carried out by transduction with a lentivirus or other retroviral vector. Viral transduction is completely expandable to allogeneic process scales, but one must consider that retroviruses are typically handled in BSL2 environments, which require proper measures and facility design for biocontainment and segregation. Aside from the safety concern, the cost and timeframe required to produce GMP-grade viral vectors are significant so it's worth considering alternative options. Electroporation methods use an electric field which temporarily permeabilizes the cell membrane, allowing for uptake of DNA into the cell. This technology started out as a cuvette-based benchtop format but has expanded into a scalable single use format offered by companies such as MaxCyte and Lonza, enabling its use in large scale allogeneic processes. As the industry continues to mature, expect to see wider adoption of electroporation instrumentation in cell therapy and viral vector manufacturing.

Looking toward the future of these life-saving therapies, raw material suppliers, equipment manufacturers, architecture and engineering firms, and drug developers all need to coordinate efforts aimed at reducing manufacturing cost and expediting delivery to patients in dire need. Process closure, end-end solutions, automation, and de-classifying manufacturing space are all strides in the right direction on our journey to make these therapies more accessible. To add more manufacturing capacity, the industry is looking beyond scaling out autologous and scaling up allogeneic processes. But one can envision a future where equipment innovators and regulators come together to enable decentralized end-end bedside autologous cell therapy manufacturing across a wider network of hospital environments.

Business

Economic drivers
Emerging trends
Business strategies

How the Energy Crisis Will Change Pharma in 2023

In the face of war and the lingering economic aftereffects of COVID-19, Europe is weathering an energy price storm. What does this mean for medicine makers?

Many of us – from ordinary families to corporate accountants – are watching our energy bills in an entirely justified state of anxiety. Stacked on top of a prolonged period of COVID-19-induced economic disruption and surging inflation, this is a tremor in the market that nobody asked for, but almost everyone will have to deal with.

So what does it mean for the pharmaceutical industry? To help us consider where to even begin, we spoke to Naomi Ikeda, a tax consultant at Ayming with a PhD in molecular biology and years of experience working with small, medium, and large companies across medtech, biotech, and pharma. Recently, Ayming published its 2023 International Innovation Barometer, which devoted roughly one third of its pagecount to the energy crisis.

What is the scope of the energy crisis right now?

The energy crisis is impacting the productivity and capabilities of many industries, not just those in the energy sector. Due to the interconnectedness of the world's industries and their reliance on fuel for production and trade, changes in one sector can have a significant impact on others, creating widespread instability across all industries. Over the years, numerous crises have had lasting effects on supply chains. Disruptions caused by the COVID-19 pandemic highlighted Europe's dependence on global suppliers and resulted in shortages of APIs and packaging materials. Continued lockdowns in China have exacerbated these shortages, while the war in Ukraine has increased the price of energy and we are still feeling the effects of COVID-19 on healthcare. This translates into simultaneous supply and cash flow shortages.

Some of these problems will affect the entire world but, in many cases, their effects will be concentrated in specific regions. The countries suffering from the energy crisis are predominantly in Europe due to their dependence on gas from the Baltic Sea pipeline – but there will also be countries outside Europe affected by the knock-on effects of the crisis. In addition, the continuing lockdowns in China have led to a significant global decrease in raw materials, increasing the costs of both consumables and manufacturing processes.

What are the knock-on effects of the crisis?

This crisis will lead to upfront corporate investment in future-proofing. This involves short- and long-term strategies for fuel saving and the creation of contingencies for further supply volatility – so we can expect some innovative benefits for the economy and the environment.

The increase in energy costs is also leading to a significant decrease in margins for European pharmaceutical manufacturers, with reports in a letter addressed to the European Commission stating that electricity prices for drug manufacturers have risen 10-fold and that costs for raw materials are increasing between 50 and 160 percent. This particularly affects products such as antibiotics, whose manufacture is energy-intensive due to the fermentation processes and required sterility. The rising costs are leading to calls for the discontinuation of generics, which would push higher costs onto the customer. This would lead to production impacts for all medication and would limit the availability of medicines for patients in need.

All of this has led many companies to seek manufacturing methods that can alleviate the pressing cost challenges. During times like these, innovation will increase as companies seek new modes of operation to create a "new normal" that is less dependent on high energy requirements.

What did the survey behind Ayming's 2023 report reveal about the energy crisis?

Our survey encompassed 846 pharmaceutical businesses across 17 different countries in Europe, Asia, and North America, and revealed numerous insights into how people across different


Naomi Ikeda

economic sectors are responding to the energy crisis. More than 80 percent of pharmaceutical companies have had to make changes to counter the rising energy bills, with 36 percent describing their changes as "radical."

Furthermore, the results showed us that pharma is less prone to inter-sector collaboration than other industries. This is most likely due to NDAs on products, which create a barrier to joint ventures and innovation. However, during this volatile period, it will be crucial for pharma to expand its collaborations.

Collaboration reduces the amount of energy each individual company requires and enables more efficient use of time and resources. During a period of ever more finite resources, the industry needs to recognize how and where redistribution of scant resources would be most useful.

More broadly, our survey showed that 41 percent of firms are looking at energy efficiency savings. Of those, 30 percent are looking at alternative energy sources, such as a new supplier or renewables, and 25 percent are looking for alternative materials that are not derived from fossil fuels. Surprisingly, only 58 percent of respondents said they were receiving the funding necessary to navigate the energy crisis, but 62 percent are expecting an increase in R&D budget. This underlines the rising importance of innovation that we can expect through 2023.

Can major private sector investments offer a way out of (or at least through) the crisis?

There are several key paths to navigate this crisis, including procurement-funded innovation within the private sector, government funding, and collaborative work within commercial sectors. However, governments must ensure that they have a wide range of support mechanisms to stimulate the energy transition, including R&D tax credits, grants, and subsidies. Effective solutions here will provide immediate benefits to both the economy and the environment and will begin to stabilize the market.

Does pharma need special support to handle rising energy costs?

During this crisis, we will need to view the interdependencies of the various sectors collectively. Pharma is just one part of a wider picture. At the height of the pandemic, pharma was the industry with the potential to save us – and it received increased attention and funding accordingly. But, in the case of the energy crisis, that responsibility is more distributed across a range of sectors. What we can say with certainty is that the danger posed by finite, geography-dependent fossil fuels has never been more real.

Across the 21st century, this danger will lead to starvation due to the lack of available resources for agriculture. We will also be faced with a lack of medicines and therapies that used to be commonplace among the general population. Ultimately, it cannot be said enough that fossil fuels contribute to increasing CO2 emissions and the rising temperature of the world, which in itself will have an ever more catastrophic impact on our way of life.

Companies that embrace greener practices reap double benefits: environmental sustainability and lower energy costs. Actioning such strategies commits funding to innovation and pays off in the long run through new savings and efficiencies. The greener a company is, the more green advances it will be able to make and the more easily it will secure additional government and commercial funding as a result.

Future-proofing by developing greener technologies is key for us all. It's these technologies that could spare us from a future riven by crises induced by our dependencies on fossil fuels and other finite resources.

Cancer Clinical Trials: The Where's Waldo? Puzzle No One Wants

Why is it so difficult to find the right candidates for oncology clinical trials?

By Selin Kurnaz and Arturo Loaiza-Bonilla, both at Massive Bio

Those of us who grew up in the 1990s will recall the phenomenon of the elusive, red-stripe-clad puzzle book character, called Waldo (or Wally, as he is known in many other countries outside the US). We spent hours seeking him out among the chaotic illustrations chock-full of red herrings. Look-alikes thwarted us as the real Waldo, carefully camouflaged, seemed impossible to spot. Today, the phrase Where's Waldo? remains pertinent to the challenge of finding eligible patients for oncology clinical trials.

More than 18 million Americans have been diagnosed with cancer in the past decade, according to the American Cancer Society (1). This is – by any measure – a staggering figure. Even with the recent Centers for Disease Control and Prevention infusion of $215 million as part of a five-year $1.1 billion grant to fund the first year of three national programs to improve cancer prevention, detection, diagnosis, and control, investment is still not being directed to fix the most fundamental problems in cancer research (2).

In particular, one huge roadblock to a cancer cure is the struggle to recruit patients for oncology trials. Approximately 80 percent of clinical trials fail to meet enrollment timelines. Two-thirds of oncology trials fold before meeting their goals due to a lack of patients, and less than five percent of adult cancer patients participate in clinical research (3). A startling analysis from

the National Cancer Database (NCDB) reveals that less than 0.1 percent of cancer patients participate in a clinical trial (4) – a trial that may hold the potential for better quality of life or even survival itself.

These sobering statistics are symptoms of a clinical research system that lacks the tools, transparency, and trust required to give hope to more cancer patients. Overcoming this biggest of obstacles is well overdue. We need to make it much easier to find Waldo.

Many obstacles hindering cancer trial enrolment

As science propels cancer treatments forward, clinical trials are increasingly designed around very small, genetically defined subsets of cancers, which, at certain stages, make finding eligible patients difficult. Researchers are tasked with enrolling patient populations that reflect the diversity of cancer demographics, further complicating patient identification. In addition, oncology trials typically require patients to have relapsed/refractory disease after standard cancer treatments at least twice before they'll be considered – in one trial, patients must have received at least three other therapies before becoming a candidate for a renal cell carcinoma trial (5).

If a patient makes it past these early hurdles, they'll find that pre-screening is strict. A recent study found that roughly 80 percent of patients with advanced non-small-cell lung cancer did not meet the criteria for the trials included in the study. As a result, 86 percent of those trials failed to complete recruitment within the targeted time (6).

Oncology trials are notoriously stringent in their inclusion criteria. In fact, 40 percent of patients with cancer trials available to them are not eligible to enroll, according to an industry report. Although these criteria are intended to ensure patient safety and create a homogenous study cohort, some industry leaders question whether cancer trial criteria are too rigid. In that same report, the US National Cancer Institute (NCI) concluded that clinical trial eligibility criteria arbitrarily eliminate patients and should be simplified and relaxed. Eligibility criteria, such as age, HIV status, the presence of previous cancers, and other criteria are being re-examined to ensure that restrictions are not unnecessarily preventing willing patients from enrolling in trials (7).

To make matters worse, many patients do not know what trials exist, how to find them, and how to determine their eligibility. Even some oncologists remain woefully unaware unless the trial is happening at their own medical site.

In addition to challenges in finding appropriate patients, two key problems exacerbate the difficulty of matching cancer trials to patients: flawed databases and disparate medical records. Electronic medical records are siloed and plagued with errors, and the process of extracting and ensuring the accuracy of information remains manual and time-consuming.

Many will agree that the de facto US database ClinicalTrials.gov is neither thorough nor easy to use. Although the database can be a powerful tool for finding trials and results reporting, it does not contain all clinical trials in the clinical research enterprise (8). Trial sponsors are responsible for updating information with little oversight by regulators, which can lead to delays and missing information. Furthermore, the database still uses industry-specific nomenclature that is difficult for patients without research experience to understand. And, although other patient advocacy group websites and larger medical centers manage newer repositories for clinical trials, these are often focused on specific cancer types or locations, which exacerbates the fragmentation of clinical trials information.

Fundamental change is daunting without better access to real-time trial availability, criteria, and reasons for exclusion, which in turn will build trust in a system that most patients see as shrouded in mystery.

A case study: technology in action

Modern technology is available to help overcome these challenges and is poised to revolutionize clinical trial recruitment.

In 2020, the National Cancer Institute (NCI) sponsored an oncology-based, clinical trial recruitment tool called a Deep Learning Clinical Trial Matching System (DLCTMS) (9). With the partnership and support of Columbia University, NCI used this software platform to optimize patient matching beginning with three trials within its National Clinical Trials Network.

Specifically, sponsors leveraged the DLCTMS to digitize all inclusion/exclusion criteria, each with multiple arms and multiple biomarkers. The system was then used to help analyze all potential barriers to enrollment and extracted patient-level data to allow for more in-depth, objective pre-screening in real time.

"Ultimately, our goal is to enroll as many patients as possible in potential clinical trials," said Richard D. Carvajal, Associate Professor of Medicine at Columbia University Vagelos College of Physicians and Surgeons and Director of Experimental Therapeutics at Columbia University Irving Medical Center. "This AI-enabled Deep Learning Clinical Trial Matching System platform is a promising solution to advance cancer clinical trial patient identification and matching."

Results to date in this ongoing study show a dramatic transformation from a fully manual, time-consuming, and error-prone set of steps into an automated and optimized digital process for active enrollment to institutional cancer clinical trials. The platform's built-in artificial intelligence technology streamlined the process, while improving patient participation and outcomes.

Nurses previously spent an average of 45 minutes per patient combing through


Selin Kurnaz

criteria to select a potential trial. The new system slashed the time to 17 seconds to screen not just one but dozens of trials. Additionally, the process of moving a patient from initial identification to consent and enrollment was streamlined from as long as 48 hours per patient to mere minutes. (This study is ongoing, see Small Business Innovation Research [SBIR] Contract No. 75N91020C00016.)

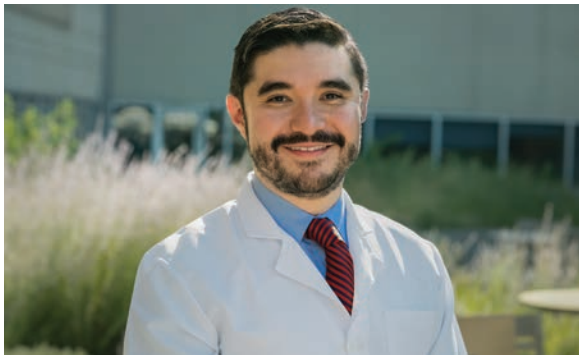
Within six months for a sample patient population, the DLCTMS helped NCI match patients to more than 111 studies with a 90 percent success rate. Since then, this technology has helped match patients to an additional 213 studies in mere fractions of traditional matching times.

The trust imperative in oncology research

The NCI's encouraging results demonstrate how modern technology can drive wholesale changes in trust and transparency that today's oncology research landscape needs. Without such technology and patient support services, connecting the right cancer patients to the right trials at the right time is like an exasperating Where's Waldo puzzle – but with heart breaking consequences. It's time for change.

It will take a broad and comprehensive effort to solve this issue. And it will also take time and demand new ways of working. But if all players in the clinical trials ecosystem – patients, providers, sponsors, payers, sites, and research organizations – center their efforts around the patient, we can transform oncology clinical trials and usher in a new era of trust in research.

Arturo Loaiza-Bonilla



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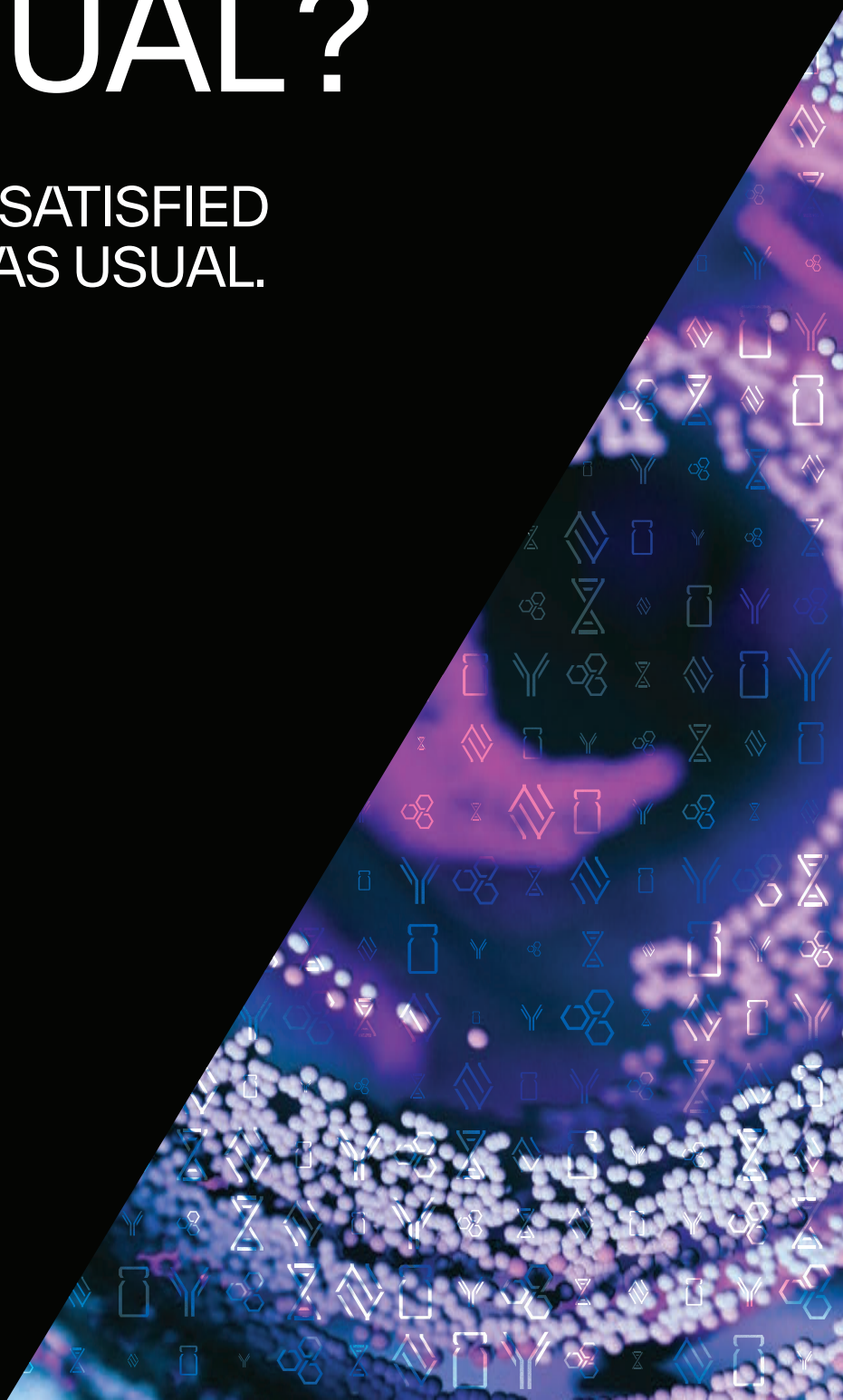


No One Left Behind

Sitting Down With… Eric Dube,
CEO of Travere Therapeutics

Did you always want to be a leader?

I actually feel like an accidental leader within the life sciences industry! I originally planned to become a physician, but when I got a job in high school working in a physician's office, I realized that the sight of blood was not for me. I had to think of other careers. I really wanted to focus on helping those who were suffering and may not necessarily feel that they have a voice. When I came out as gay at the age of 18, it was the height of the AIDS epidemic and there wasn't a lot of innovation in this space. I decided not to go into medicine, but to go into behavioral health – it was very important to me to have a good view of how to advocate for your health, your identity, your needs, while recognizing the strength of the community.

I worked in academia for a while before moving into the pharma industry. Initially, I didn't think I would stay long because I sensed there wasn't a tremendous amount of collaboration between the industry and government, or the industry and patient communities – both of which I think are important. As a behavioral scientist, my default view is to think about patients as humans with families – and how we can serve them with the work we do. This view tends to stand out in pharma and biotech as rare.

How did it feel to step up as a CEO?

The opportunity with Travere was unique and suited my experiences. But I confess – it was nerve wracking! No matter what incredible experiences and training you have, it's very different when you move to the role of CEO – particularly at a small company. I asked myself many questions. Was I ready? Was I the right person? I had to constantly tell myself, "I can do this!" And remind myself that there was a talented team and a very supportive board. I joined the company in early 2019 but then the pandemic arrived. In a way, it was a great leveler; even CEOs who had been in the role for 20 years did not have a playbook for that!

How is the company being innovative?

Well, I'd say we have tried to reset the expectation for how biotechs work. So much of what the industry does is proprietary and competitive – but one way we will bring innovation to a suffering community is to collaborate rather than compete. I really would love to see more people in CEO seats genuinely thinking about ways in which we could work together more. For example, within six or so months of joining Travere, we had an investigational therapy in phase III that failed, forcing us to shelve the program. A Travere team member working on that clinical program at the time told us that we could not give up; she suggested that we donate the dataset. So, rather than lock the data and experience away in a filing cabinet, we donated the dataset to academia and to another company that had been a competitor. In this way, we might be able to increase the probability of success for another therapy for this rare disease. I wish there were more examples like this in the industry.

What is the best advice you have ever received?

In my first few years at large pharma, I would often be told that I was doing great when I received feedback on my performance. But I was also told that I wasn't tough enough or that I was too soft. This didn't resonate with me well as a gay man because I felt like I was acting true to myself. Fortunately, there was one leader who I could have an open conversation with and she gave me some great advice. I had to make a conscious choice: am I going to adhere to what people expect? Or am I going to advocate for what I believe in? She told me to be the leader that I wanted to be. This advice changed how I thought about myself as a leader and I have never regretted it.

I am proud to say that, yes, I am going to care about people. And in recent years,

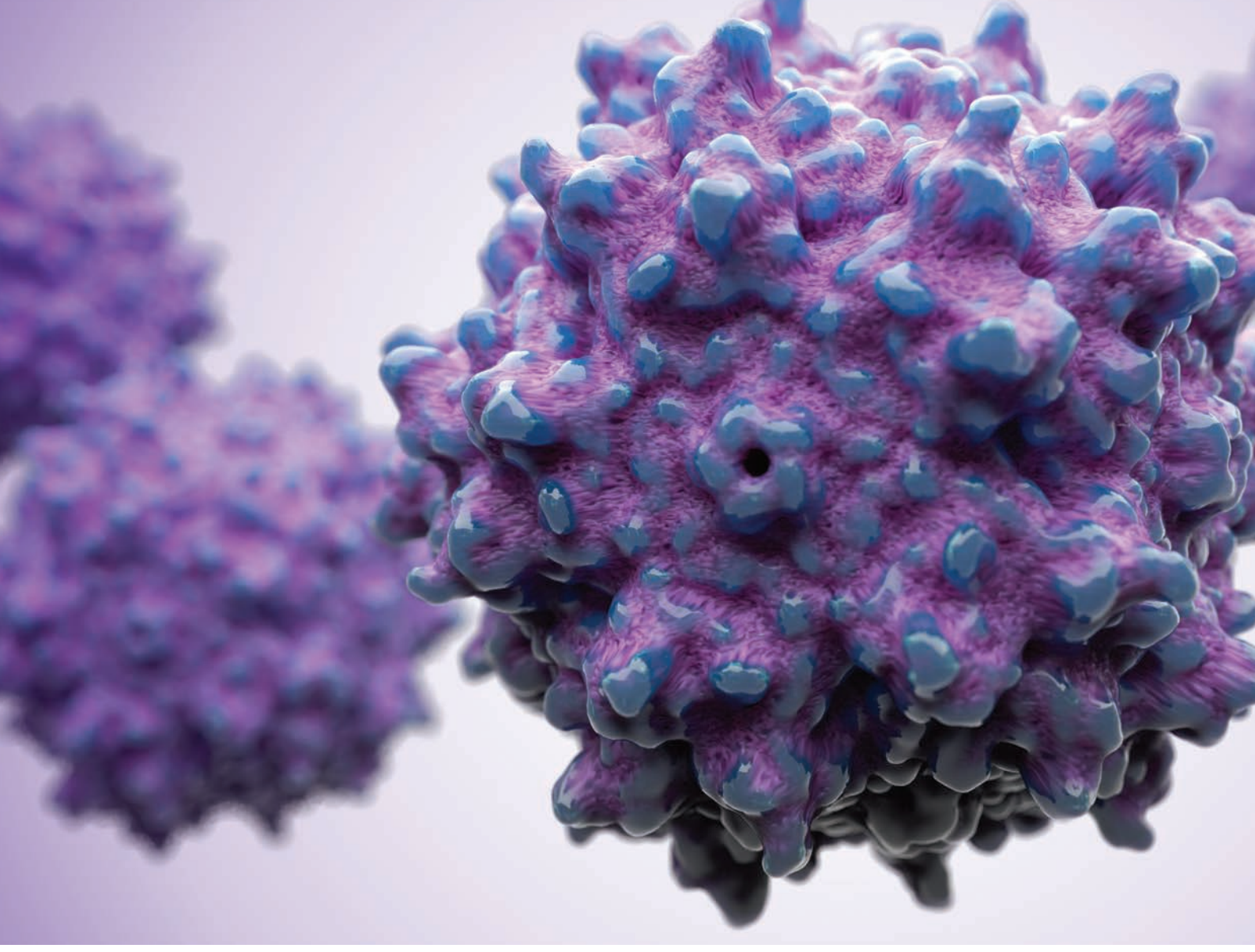
"No matter what incredible experiences and training you have, it's very different when you move to the role of CEO."

I think views on leadership have changed and the traditional style or phenotype of leader has been challenged as we think about how people want to work post COVID-19 and what younger generations want. In fact, many of the traits I was told were weaknesses in leaders are now seen as strengths as we emerge from the pandemic.

And how do you lead?

I aim to foster a sense of belonging in the company, and I also believe that everyone should be able to show up and be the type of employee or leader that is most natural for them. I was certainly the benefactor of this advice and I want to make sure that I can do the same for the next generation of leaders.

One of the pieces of advice that I consistently give to our employees is this: "Be kind to yourself, and be kind to one another." Biopharma is not an easy industry. We are faced with constant challenges, failures, and setbacks on a regular basis as part of the scientific process. We have to make sure that we are kind to ourselves and do not let the negativity get us down. I also tell people that we have to be persistent; families are counting on us and we have to pick ourselves up and find a way forward, regardless of whatever challenges or barriers we face.



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