NOVEMBER / DECEMBER 2023 # 94

the Medicine Maker®

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INNOVATION
Awards

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16 – 24

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2023: A Year to Remember

From packaging to genome editing approval, 2023 was a good one for the industry

The close of the year is an apt time for reflection. For the pharma industry, there is a lot to look back on with pride. The year 2023 saw the mRNA technology behind key COVID-19 vaccines recognized as a Nobel Prize winning innovation. The way it changed the course of the COVID-19 pandemic was swift – as is often the case with meaningful innovations. In the wake of that change was ongoing dubiety and controversy with a little anti-vax rhetoric thrown in for good measure. Not everybody can keep up with the speed of science, it seems. I hope the post-pandemic lessons learned extend to a more accurate and effective means of introducing the world to such developments.

Another incredible moment snuck into 2023: the world's first approval for a CRISPR-Cas9 gene editing therapy. At the time of going to print, Casgevy has been approved by the UK's MHRA with an imminent decision expected from the US FDA. Casgevy is a biotechnology product licensed to Vertex Pharmaceuticals and CRISPR Therapeutics for the treatment of sickle-cell disease and beta-thalassaemia. Speaking in November, CEO of the UK Sickle Cell Society John James OBE said, "I welcome today's news that a new treatment has been judged safe and effective, which has the potential to significantly improve the quality of life for so many."

Stepping away from therapeutic modalities, I've also spotted an interesting innovation in the packaging sector. With consumers having mastered the disruptive technology of smartphones, leaders at Bormioli released a call this year for innovations in childproof and child-resistant packaging. The winning innovation came from a group of researchers based in Lima, Peru, who presented the Turn-It project: a cap that can only be opened if the named patient provides a biometric scan of their registered fingerprint via an app. Not only might this help reduce the number of cases of minors gaining access to medicines, it will improve the ability of elderly and infirm patients gaining access. Combining child-resistant packaging with ease of use for the elderly has been an ongoing dilemma for packaging designers!

Our celebration of innovation will continue into the next issue, where we look at some of 2023's highlights in Industry 4.0. An annus mirabilis for the industry? Judge for yourself as you read on – this year's Innovation Awards nominees can be found on page 16.

Rob Coker
Deputy Editor

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the Medicine Maker

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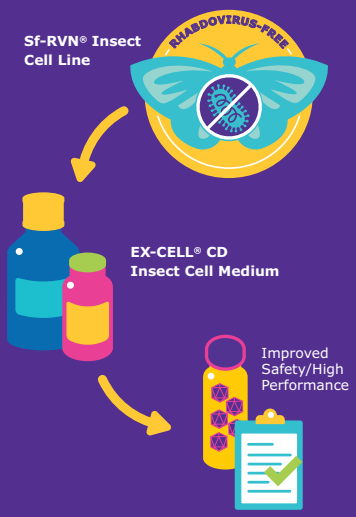

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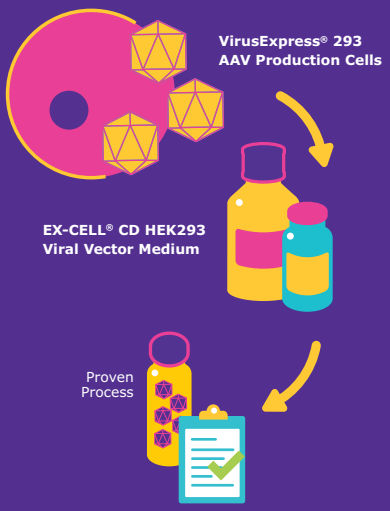

For LV Production

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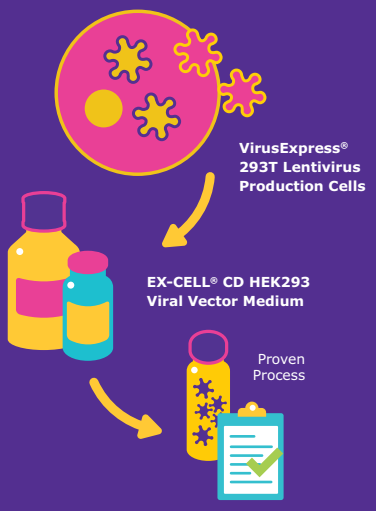

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One Vaccine to Rule Them All

Can we protect patients against multiple healthcare-associated infections in a single shot?

Healthcare-associated infections (HAI) are an ever-present concern. Statistics suggest more than 90,000 lives have been claimed in the US alone from HAIs, with costs reaching into billions of dollars (1). Today, approximately one in 31 hospital patients falls victim to these infections, and though progress has been made in preventing various types of HAI, there is still much work to be done.

Standard infection treatments are limited because most HAIs are caused by pathogens that have developed resistance to antimicrobials – but could vaccines offer a ray of hope? Possibly – with a caveat. "Even if there were such vaccines, multiple vaccines would have to be deployed simultaneously to protect against the full slate of antibiotic-resistant microbes that cause healthcare-acquired infections," said Brian Luna, an assistant professor of molecular microbiology and immunology at the University of Southern California (USC), in a statement (2).

Change could be on the horizon, however, as USC researchers recently reported promising data from preclinical in vivo studies focused on a vaccine designed to shield patients from multiple nosocomial pathogens at once (3). The study showed that a single dose of the vaccine in mice transformed immune cells into "Incredible Hulk" mode and provided rapid protection against eight different drug-resistant bacteria and fungi.

"It's like Homeland Security putting out a terror alert," said senior author Brad Spellberg, Chief Medical Officer at the USC-affiliated Los Angeles General Medical Center. "Everybody, keep your eyes open. Keep an eye out for suspicious packages. You're alerting the soldiers and tanks of your immune system. The vaccine activates them."

The vaccine contains three ingredients – two are already used in FDA-approved vaccines and the third is a small piece of fungus often found on human skin. The combination was found to effectively stimulate the body's supply of macrophages against HAIs, curbing the threat of replication.

Even in cases when infections did develop, vaccinated rodent survival times were longer than unvaccinated controls. Moreover, the vaccine took effect within 24 hours, with protection lasting for up to 28 days. According to the team's testing, only five percent of hospital stays last longer than three weeks, and early data suggests a second shot could extend the protective window for those in the hospital for longer periods.

Moving forward, the researchers hope to receive FDA guidance on the requirements to complete preclinical studies and an Investigational New Drug Application by 2024.

This article originally appeared on our sister brand, ID Transmission

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TIMELINE

Another Year of Innovation

A look back at some of the top FDA approvals of 2023

January

Leqembi (Eisai; accelerated approval for monoclonal antibody for Alzheimer's disease)

February

Jesduvroq (GSK; oral treatment for anemia of chronic kidney disease)

March

Skyclarys (Reata Pharmaceuticals; treatment for Friedreich's ataxia)

REATA PHARMACEUTICALS

April

Qalsody (Biogen; accelerated approval for treatment targeting genetic cause of ALS)

BLOGS-IN-BRIEF

Preventing opioid relapse, artificial lifeforms, and CRISPR chickens… Here's the latest from our blogs

- Sound sleep is an indicator of good health, but recent research from scientists at the Scripps Research Institute hints at its potential to prevent opioid relapse. More specifically, they explored the potential benefits of treating opioid withdrawal using an experimental insomnia drug known as DORA-12. The drug is a dual orexin receptor antagonist.**tmm.txp.to/opiate-relapse-drug**
- Contaminated cough medicines and the deaths of young children continue to make media headlines. The Indian drug regulator has reportedly identified more dangerous products. DEG and EG have also been mentioned in recent FDA warning letters, and the IPEC Federation has updated its position paper on the topic. **tmm.txp.to/deg-eg-contamination**
- Two professors claim to have developed a nanoscale-sized artificial hybrid molecule that could, artificially, generate life-forms. The field of research is called hybrid peptide-DNA nanostructures – and is less than a decade old. The researchers aim to create modified viral vaccines and transplant them into a "host" that could keep other viruses in check. **tmm.txp.to/sci-fi-to-life**
- Scientists at Imperial College London, the Pirbright Institute, and the University of Edinburgh have used CRISPR/Cas9 to generate gene-edited chickens resistant to bird flu. All subtypes of the bird flu virus rely on "hijacking" a protein called ANP32A. The researchers edited two amino acids in ANP32A to stop the virus in its tracks. **tmm.txp.to/crispr-chickens**

Celebrating a Century

Novo Nordisk injects $6 billion to upgrade its Kalundborg facility

Novo Nordisk is marking its 100th anniversary with an investment of over $6 billion into an existing manufacturing facility in Kalundborg, Denmark. The vast majority of the investment will go towards increasing the manufacturing capacity of the company's key active pharmaceutical ingredients, including semaglutide, which is used in injectable diabetes medications, such as Ozempic and Wegovy, as well as the oral variant Rybelsus. The investment also includes a new 170,000 square-meter facility to make multiple products and accommodate future processes. The first construction project is expected to be complete by 2025, with further finalizations expected through to 2029. Once the new facilities are fully equipped, Novo Nordisk is expected to create 800 new jobs. The company's total manufacturing footprint in Kalundborg will eventually exceed 1.6 million square meters.

May

Arexvy (GSK; RSV vaccine for older adults)

June

Elevidys (Sarepta; gene therapy for Duchenne muscular dystrophy)

July

Beyfortus (AstraZeneca and Sanofi; drug to prevent RSV in neonates and infants)

Leqembi accelerated approval converted to traditional approval

August

Zurzuvae (Sage Therapeutics; oral treatment for postpartum depression)

November

Zepbound (Eli Lilly; treatment of obesity)

By Franz Eugen Köhler, Köhler's Medizinal-Pflanzen - List of Koehler Images The Internet Archive, Public Domain, Wikipedia.

MIA and Potent Plants

Can genetically engineered yeast be used to produce safe, scalable, plant-inspired schizophrenia drugs?

The use of herbal medicine can be traced to many ancient civilizations, with the earliest written records dating back approximately 5,000 years. Even today we turn to the power of plants for inspiration if not for direct therapeutic effect." Development of medicines from natural plant substances is widely used. However, since plants do not produce these substances to fight human diseases, there is often a need to modify them to make them more effective and safe," said Michael Krogh Jensen, a senior researcher at DTU Biosustain and co-founder of the biotech company Biomia, who is exploring the potential of plant-inspired compounds for the treatment of schizophrenia (1).

Previous research indicated that plant monoterpene indole alkaloids (MIAs), such as alstonine and serpentine, possess potent antipsychotic properties, pointing to potential therapeutic use for mental disorders. However, scaling has been a challenge. But now Krogh Jensen and a team of international researchers have developed a scalable platform to perform de novo biosynthesis of serpentine and alstonine – using yeast (2).

"We have found a method to make yeast cells use enzymes and carry out the same chemical process that takes place in halogenation. Plants generally can't naturally carry out halogenation. Therefore, our versatile biotechnological platform is a possible method for optimizing and developing plant-based alkaloids that may then be used to make medicines against, for example, schizophrenia."

And there certainly is a need; current therapeutic options for schizophrenia effectively target delusions and hallucinations but fall short in fully addressing cognitive impairment. Moreover, these treatments can result in "negative side effects such as insomnia, weight gain and reduced immunity," according to Krogh Jensen.

The team's research into yeast-based manufacturing of 19 different plant-inspired but "new-to-nature" haloserpentine and haloalstonine analogs is ongoing, but Krogh Jensen hopes the engineered candidates will find their way into various clinical trials by 2026.

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A United Front

Biotech companies join together to advocate for global mRNA innovation

A group of 31 biotechnology, biopharma and life science companies, along with educational institutions, have recently launched the Alliance for mRNA Medicines (AMM). The initiative was unveiled at the International mRNA Health Conference in Berlin, Germany, and will be dedicated to advancing global mRNA innovation by advocating for the sector's key policy priorities across legislative and regulatory bodies in North America, Europe, and Asia. The AMM also aims to foster collaboration among scientists, policymakers, companies, governments, and patients to overcome obstacles in mRNA research, development, and manufacturing. "With the founding of the Alliance for mRNA Medicines, our community is now poised to champion scientific standards and public policies that will spur future mRNA breakthroughs – from halting chronic disease to erasing cancer," said Andy Geall, Chairman of the AMM Board and Co-Founder and Chief Development Officer of Replicate Bioscience.

IMAGE OF THE MONTH

To Boldly Cardio

A team of scientists have taken their research to new heights by leveraging the International Space Station National Laboratory to investigate the impact of microgravity on heart cells. Here, NASA Astronaut Kate Rubins examines iPSC-derived cardiomyocytes grown within a fully enclosed cell culture plate.
Credit: Image courtesy of NASA

Would you like your photo featured in Image of the Month?
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QUOTE of the month

"Today is a historic day in science and medicine: this authorization of Casgevy in Great Britain is the first regulatory authorization of a CRISPR-based therapy in the world."

Reshma Kewalramani, CEO and President at Vertex Pharmaceuticals, discusses the conditional marketing authorization from the UK's Medicines and Healthcare Products Regulatory Agency for Vertex and CRISPR Therapeutics' Casgevy.

Tying Up Loose Ends

Companies face a crackdown after a new Federal Trade Commission initiative

The Federal Trade Commission (FTC) has announced a new initiative to curb what it deems as "improper" patents listed in the FDA's Orange Book. The Commission is taking action against over 100 patents related to drugs from major companies, including AbbVie, AstraZeneca, Boehringer Ingelheim, GSK, and Teva. The FTC contends that such listings can obstruct competition in the drug industry. To date, FTC has dispatched letters to 10 companies, initiating patent disputes and emphasizing the hindrance that improper patents pose to regulatory processes and legal challenges for generic drug manufacturers. Notable medications affected by this crackdown include AbbVie's Restasis and Viatris' EpiPen autoinjectors. Drug manufacturers facing challenges have a 30-day window to either amend or withdraw their patent listings or assert, under penalty of perjury, the legitimacy of the patents.

By Carol M. Highsmith (born 1946) - Photo from the Carol M. Highsmith collection, reproduction number LC-DIG-pplot-13734-01527, Public Domain, Wikipedia

Say No to Subpar Slurry Preparation

Discover how Asahi Kasei Bioprocess is engineering a streamlined approach to chromatography media preparation.

Should we, as an industry, settle for bureaucratic inertia when better options exist? This is the very question Asahi Kasei Bioprocess (AKB) is asking downstream process operators. To date, bioprocessing has relied on manual, time-consuming strategies in chromatography media preparation. However, alternatives do exist. Meet SLURIPREP™, a media preparation and column charging system that can upgrade purification processes.

To learn more, we spoke with Steve Foy, Manager of Products and Brand Strategy at AKB, which not only provides bioprocess equipment and consumables, but also scientific support.

What is your role at the company?

My primary goal is to understand both our products and customers – and then to ensure we pair strategic goals and customer needs with concrete measures. Day-to-day, I work alongside our interdisciplinary team of scientists and engineers to communicate what our customers and the market need at large. I do this by working closely with customers, answering their questions and discussing their interest areas. Once a project starts, our engineers and project managers interface often with our customers to make sure they get exactly what they need, on time and as promised.

How do companies typically approach chromatography media preparation?

Chromatography media receives a lot of attention, but not always for the right reasons – it's expensive and companies must mitigate wastage. Most importantly, the preparation and mixing processes are still largely performed manually which, again, is not terribly efficient and can lead to extended equipment downtime. And despite there being alternatives to manual preparation, the demanding regulations of the manufacturing environment can make pharma companies reluctant to implement new technologies. In biomanufacturing, much focus goes on the final product, but there is a lot to be gained by looking at chromatography media.

Take buffers, for example. These are essential throughout biomanufacturing, particularly downstream. For years the standard industry approach has been to prepare buffers manually (a highly labor-intensive and inefficient approach) and store them in large tanks, which takes up a huge footprint within the facility. Because buffers are ubiquitous in the industry, the process can sometimes be overlooked in terms of seeking further optimization.

Sacrifice for future gain is something we should become more comfortable with as an industry. By investing time in a new strategy for slurry preparation specifically, you can streamline processes and be more productive.

What are the consequences of incorrect media preparation?

There are several kinds of chromatography media, with silica gel being one of the most popular. The media arrives at the facility in containers that are usually premixed with buffers, and then operators will often prepare the slurry manually before dumping it into a receptacle or column to get them packed. This is not a quick process; it involves a lot of labor and is tedious – and resettlement can occur within the column before you begin packing. In chromatography media, the beads themselves can settle to the bottom while the liquid rises to the top. This is not dissimilar to when you buy orange juice at the grocery store – the pulp may have settled to the bottom so that you have to mix it up before pouring it into your glass. Also, if mixed incorrectly, the optimization and efficiency of the bed pack can be affected.

When handling media, particularly silica, it's also important to be gentle. The material can withstand pressures within the column (if applied evenly), but the beads can break if shaken improperly, or prepared incorrectly. This can lead to fines – essentially very small shards of glass – which will settle at the bottom of a container or column. And though the fines won't necessarily make their way into the final product, they can clog column frits more quickly and decrease batch productivity.

Some purification media can arrive at a bioprocessing facility in the form of powder, the preparation of which requires additional steps – such as hydration

AsahiKASEI BIOPROCESS

– and the use of personal protective equipment since the powder can become airborne. Once again, manual methods for preparation can be tedious and lengthy.

What are the benefits of SLURIPREP?

So the saying goes, "An ounce of prevention is worth a pound of cure." And it holds true in the face of media preparation. The industry lacks awareness of viable alternatives to the manual-centric methods of media preparation, but the technologies do exist. It may take training to use a new approach, but in the long run, you will operate with enhanced capacity.

AKB's SLURIPREP Systems (SPS) can be provided as ancillaries to our liquid chromatography systems and columns. These systems have large tanks and are driven by air pressure. They do not require electricity, which means they are usable in hazardous areas. Once you have your container of media, all you need to do is mix it, then pour it into the SPS. The agitator homogenizes the media gently and circulates it. You can also decant fines.

Because the system is connected to the column, packing and pressurization can occur very quickly, leaving less time for anything to resettle. This helps maintain a balanced mixture and allows for a more homogenized packed bed – and thus, a more efficient purification process.

We have been offering our SPS equipment to customers for years, but we are now expanding the technology by launching the SLURIPREP Mixer, which can combine the media gently within the container received from the manufacturer. This device can also pull the slurry into the SPS itself, allowing for further preparation. Fundamentally, it helps ensure that the media is as optimized as possible before moving onto packing.

SLURIPREP allows for an entirely closed process – hazards such as spills and airborne powder are reduced, improving operator safety, and increasing productivity.

What feedback have you had from customers?

At AKB, we focus on mitigating the logistical challenges that surround drug development. And the demands of customers are clear: increase productivity using safe and reliable systems that are (relatively) easy to operate. These demands have largely informed our practice. Our customers have been aware of the benefits of SLURIPREP for years, but in the wider market, there is less awareness of alternatives to manual methods. It's important for the market to know that not everything has to be done manually.

We have received overwhelmingly positive feedback regarding SLURIPREP's functional use. Being mechanical and driven by pressure, there are no requirements to learn new software. Other positives relate to the system's capacity to minimize labor hours. In fact, we've found a single operator can use SLURIPREP, as opposed to several preparing media manually.

Customers are also pleased with the customizable nature of our products. For example, the typical SLURIPREP system is up to 600L, but this can be customized to 1000L if required. In addition, our preparation systems are attached to (or correspond with) columns from anything between 30 to 120 cm in size, which includes compatibility with low, medium, and high pressure liquid chromatography requirements.

Ultimately, we want to develop strong partnerships with customers and, to do this, we require a clear understanding of what companies want. This is dependent on knowledge sharing; we must communicate to create high-quality products for the benefit of patients. In terms of SLURIPREP and preparing chromatography media, we are directly focused on incremental gains to optimize production and internal efficiency.

What lies ahead for AKB?

Asahi Kasei Bioprocess has a clear mission: "to build strong partnerships and innovative equipment in pursuit of helping deliver medicines that patients can trust." We are immensely proud of our products, but in alignment with our purpose, we are always looking for ways to improve the processes that underpin successful drug development.

https://fluidmgmt.ak-bio.com/

In My View

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

Shouldn't We Modernize Quality Control Operations?

Three steps to drive meaningful change in QC

By Jason Boyd, Senior Director, Vault LIMS strategy at Veeva Systems

As the rapid growth of QC digital projects continue to raise lab efficiency standards, more and more QC leaders are turning to stand-alone applications – software that doesn't come bundled with other independent software features. The reason for this is that business users in the lab are solving single problems at a time. Subsequently, they need to bolt single use and stand-alone applications into their existing ecosystem. For example, if their laboratory information management system (LIMS) does not provide a pathway to full digital method execution, they will implement an electronic laboratory notebook and interface it to their LIMS.

However, these applications often need to be tailored to each individual project, which can lead to a disjointed setup with individual labs using different tools to execute processes. Without a holistic quality data and workflow view, these solutions are simply not optimized for connectivity and unification.

If quality leaders wish to drive meaningful change in QC and adopt the right systems, then there are three steps that I would recommend.

First, you need to address the actual problem. Never start with a mindset of "we need this specific tool" without first looking at the challenge you need to solve! There are many different QC solutions out there and you need to identify the one that will work for you. Often, QC in pharma includes a mix of manual processes that rely on paper, spreadsheets, homegrown solutions, and vendor-provided point solutions. You should look at the complete quality ecosystem and evaluate the opportunities for improvement. For example, if analysts use various systems to upload and download files across several departments, a single document repository for all document collaboration can relieve some of the pain users experience in terms of daily logging in and out and choosing the right system for each document type.

Mapping out end-to-end business processes can also help leaders determine what systems or activities need to be streamlined. This process helps assess what to keep, what to expand, and what to decommission.

"Never start with a mindset of 'we need this specific tool' without first looking at the challenges you need to solve."

Key considerations include whether the applications currently being used are sustainable, drive cost savings, and align with the organization's roadmap.

Second, don't just leave it to one person or department! You'll need a team to help you with the big decisions (and any potential bumps you may encounter down the road). It can also be worth involving external consultants and firms to make sure you get everything right. Assemble a team representing the complete quality business process to define an achievable timeline, prioritize capabilities, and establish a strategy for organizational change management.

Third, choose your solution. You must decide whether building or buying technology makes the most sense. Developing a matrix for technology selection that encompasses current and future needs, as well as existing products, services, and support can drive the conversation forward. When evaluating technology, don't forget to consider useability. Look at the user experience, access to information (anytime, anywhere access to data is always preferable), connectivity with other systems, and automation of time-consuming, tedious tasks.

You'll also need to look at master data management. For systems to interface together well, they need to share context about product hierarchies, market definitions, testing methods, and evaluation criteria. Master data harmonization is the key to this and can help to link systems, like LIMS, manufacturing execution system, asset management, and enterprise resource planning.. You should determine the level of harmonization for master data within the project and select systems to be publishers and consumers of data definitions. The system should also provide the flexibility and agility to support your long-term data interface strategy, without requiring an exhaustive upfront investment.

It goes without saying that you should also look at the reputation of the vendor you are buying from!

Having a connected solution for all quality data and documents will end the "we don't know what's where" conundrum, which often occurs when employees are working with disparate QC systems. It will also find yourself aligned with steadily growing awareness of the value of connected systems; the LIMS market is projected to hit $3.5 billion by 2030 – driven significantly by a desire to transform QC lab operations.

I would encourage all companies to take a long, hard look at their QC operations. If change is necessary, build a team of key stakeholders and go through a rigorous evaluation process for technologies that can help. This strategy can not only optimize lab management, but also accelerate batch release and help you get more value from your QC processes.

The FLEET of Hope

Fungal infections and antifungal resistance are a significant problem; here's one approach to consider

By Robert H Cichewicz, Principal Investigator and Regents Professor in the Department of Chemistry and Biochemistry, Dodge Family College of Arts and Sciences at the University of Oklahoma, USA

Nature has a way of endlessly probing what is possible, including coming up with new ways to negate the effects of antifungals. It is an endless process as old as life itself; it's a fight that humans will always face. Fungal infections account for the death of thousands of Americans each year – some with a staggering morbidity rate of near 80 percent.

Today, only a handful of antifungal treatments are available and, to make matters worse, they are becoming less effective. Moreover, fungi share more cell biology with humans than humans do with bacteria, making the process of chemically targeting them quite challenging. In short, new and reemerging fungal pathogens are a real threat to human safety, as well as a risk to our food security (fungi causes massive losses in agricultural settings).

As new medical breakthroughs occur, we see a trickle-down effect in which other diseases become more prevalent. For example, cancer chemotherapies often wreak havoc on immune system function, which results in many bouts of fungal infections in those undergoing cancer treatments. Basically, any situation that reduces the capacity of how our immune systems work will put us at increased risk of serious and life-threatening fungal infections. These issues represent a small handful of the challenges humanity faces in its efforts to reduce the economic burden and loss of life caused by fungi.

Accordingly, our team wanted to explore various intersecting interests that could help the field develop; namely, building a collection of endophytic fungi, exploring antifungal drug discovery, and investigating complex natural product structures. One molecule we were particularly excited by was persephacin. It first appeared in our screening of leaf samples for endophytes. In this case, the fungus that makes persephacin was killing the other fungi growing around it – an ability we believe can translate to the needs of humans for controlling fungal growth in our bodies, animals, and plants. Many current anti-fungal treatments are toxic to the human body, but we found that persephacin was reasonably non-toxic to human cells.

"Today, only a handful of antifungal treatments are available and, to make matters worse, they are becoming less effective."

We then hypothesized that if persephacin could help plants fight off infections, other molecules found on leaves might also protect humans and animals from fungal pathogens. To test this, we developed a novel way to procure leaf samples using a laser device called the Fast Laser-Enabled Endophyte Trapper (FLEET). Simply put, the FLEET system was our answer to the issue of preparing large numbers of samples for obtaining endophytic fungi. How did we come up with this approach? Well, I was traveling on a plane, contemplating leaf samples, when, all of a sudden, lasers came to mind. Not long after, the FLEET system was fully functional!

Using traditional methods, we could process roughly four to six samples per minute, but our FLEET system is capable of generating between 500-600 tissue specimens in 10 minutes. This allows us to rapidly screen more samples and enhances the opportunity for potential drug discoveries. Fungal research demands working in an aseptic manner – to limit or avoid the introduction of new germs; touching samples is one way to introduce contaminants, so the more we can avoid contact with the sample, the better.

Our next big task is to figure out what fungal pathogens to go after with persephacin, while assessing the whole range of factors that go into understanding the optimal methods for making the molecule at a large scale. We also need to assess the pharmacokinetics, metabolism, adsorption, distribution, excretion, and activity in vivo. Finally, we also need to look deeper into possible warning signs of yet-to-be-identified toxicity.

This project was just the start – but we already have new and exciting potential treatment. With FLEET, who knows what other undiscovered molecules lie waiting round the next corner (or leaf).

Droplet Digital PCR Technology for Accelerated Gene Therapy Testing

Dipika Gurnani, Global Product Manager of Droplet Digital PCR (ddPCR) Biopharma Solutions at Bio-Rad Laboratories, explains why gene therapy developers are turning to the advanced technique for rapid detection of replication-competent viruses

How is the space of development in AAV gene therapies affecting conversations around testing?

AAVs are the most commonly used vectors for gene therapy because they are effective carriers of genetic information and are naturally safe. They persistently express the transgene product in non-dividing cells, possess a low immune profile, and, in some cases, direct the immune system to tolerate transgene products.

However, AAVs also present challenges for manufacturers – not least the issue of producing functional vectors in sufficiently high concentrations. There are also a host of impurities and contaminants that can complicate AAV development in general, so implementing the best quality measures is important to help drive the field forward.

Of particular concern is the presence of replication-competent AAV (RCAAVs), which can affect a therapy's quality, efficacy, and safety – in the worst-case scenario, their presence could lead to a patient's death. RCAAVs can also result in contamination of manufacturing facilities. Most current gene therapy approaches use vectors that have been modified to be replication incompetent, but RCV testing is still required by regulators to ensure safety.

Which methods are typically used for RCV testing?

In-process testing requires culture-based methods, which can take 30–45 days to deliver results. Developing RCV testing assays with high sensitivity and specificity can be challenging; moreover, the labs running the tests need to be at least biosafety level two.

For lot release – where turnaround time is crucial – regulators have draft guidance that allows the use of nucleic acid-based methods, such as quantitative PCR (qPCR) and digital PCR. When using these methods, you must ensure that i) the primers and probes used have the correct sensitivity, and ii) they will not lead to false positives or false negatives. Validating these assays, primers, and probes can be resource-intensive and time consuming.

Why is ddPCR technology such a powerful technique for gene therapy testing?

Traditionally, qPCR has been the go-to method, but in terms of overall workflow efficiency in biopharma – and getting results that are fast and reproducible, without compromising on sensitivity or specificity – ddPCR is the technology that innovative companies are now adopting.

If you are using qPCR, you must first conduct DNA extraction. Additionally, qPCR involves relative measurements, so a reference point is required, which is achieved by running a standard curve. In a regulated context, standard curves may not appear to be difficult, but they can be expensive and tiresome to maintain over time.

On the other hand, ddPCR technology is both very sensitive and highly specific, providing absolute quantification. Each 20 µl sample is partitioned into 20,000 droplets – that's nearly two million partitioned PCR reactions in a 96-well plate – and each droplet yields a positive or negative result. Once the droplets are generated, PCR is performed to the endpoint. After amplification, the droplet reader then counts which ones are positive compared to the negative ones. If a droplet contains a target copy, it is considered a positive droplet and will exhibit increased fluorescence, whereas a droplet without a target copy is considered negative and will exhibit little to no fluorescence. The ratio of positive droplets to negative droplets is then analyzed using Poisson statistics to determine the concentration of the DNA template in the original sample.

What innovations are emerging in the ddPCR space?

Over the years, Bio-Rad has launched various contamination testing kits, including mycoplasma and residual HEK293 DNA. Recently, we have introduced replication-competent AAV and replication-competent lentivirus kits, which provide results within eight hours. We hope that these kits will help accelerate safety testing for gene therapy companies.

Our objective is to offer standardized kits that can be adopted and compared across different laboratories; as confidence builds in the consistency and reliability of these kits, we believe it will facilitate regulatory acceptance.

BIO-RAD

www.bio-rad.com/ddPCR-Vericheck-RCV

the Medicine Maker

INNOVATION *Awards*

December is upon us once more – and that means it's time for The Medicine Maker to showcase the most innovative technologies of the past 12 months.

This list is built on nominations received via The Medicine Maker website – but which innovation leads the rest? It's up to you to decide. Simply peruse the summaries on the following pages and then complete the online form: tmm.txp.to/innowin23

Voting will close on March 4, 2024. The winner will have the opportunity to share the story behind their innovation in a 2024 edition of The Medicine Maker.

Without further ado, welcome to the 2023 Innovation Awards!

CELL SHUTTLE

Fully automated, end-to-end robotic cell therapy manufacturing platform

Cellares

Cellares' Cell Shuttle robots have been used by some companies through an access scheme, but they are now more widely available. Cell Shuttle robots are self-contained units capable of executing all cell therapy manufacturing processes, including cell enrichment, sampling, selection, expansion, gene transfer, and formulation. According to Cellares, automation of these steps can reduce costs by up to 65 percent, minimize labor and facility space requirements by up to 90 percent, and lower process failure rates by as much as 75 percent. Cell Shuttle technology is also housed within integrated development and manufacturing organization "smart factories," which, according to Cellares, have the capacity to produce ten times the number of cell therapy batches per year compared with traditional facilities – all within the same physical footprint and workforce.

CLEANCAP M6

Capping technology designed to overcome legacy limitations

TriLink BioTechnologies

TriLink says that its CleanCap M6 mRNA cap analog can help developers and researchers maximize the impact of mRNA therapeutics and vaccines, all while reducing manufacturing costs. A 5' cap structure is integral to the stability, expression, and immunogenicity of an mRNA product, but generating a synthetic cap can present manufacturing challenges and inefficiencies. The CleanCap M6 analog improves potency and increases mRNA yields with a capping efficiency of more than 95 percent. Specifically, it produces a natural Cap 1 structure, reducing immunogenicity and increasing mRNA expression by 30 percent compared with legacy capping methods. The technology's single-pot reaction also requires fewer manufacturing steps, allowing quicker turnaround times, scale-up, and higher transcriptional yields.

As mRNA therapeutic and vaccine pipelines continue to evolve, efficient manufacturing will prove to be critical. Different capping methods impact how efficiently manufacturers can produce a vaccine or therapeutic product because capping reagents influence both downstream and upstream processes affecting cost, time, yield, and purity.

ENPROTECT

Two-layer capsule with enteric delivery and acid protection performance

Lonza, Capsules and Health Ingredients

Enprotect is a bi-layer capsule developed to assist in acid protection and enteric delivery of drug modalities. The hydroxypropyl methylcellulose (HPMC) inner layer provides the appropriate properties for forming a hard capsule in terms of manufacturing process and mechanical properties, while the hydroxypropyl methylcellulose acetate succinate (HPMC-AS) outer layer ensures it opens or disintegrates in the small intestine rather than the stomach – thus providing targeted enteric delivery and protection of the contents from the upper gastrointestinal tract fluids.

According to Lonza, the innovation was made possible by a breakthrough manufacturing platform technology that can produce capsules with two distinct layers while maintaining the standard dimensions of a two-piece hard capsule. The manufacturing method does not require an enteric coating formulation or process parameter. In addition, there is no stress to sensitive APIs because they are filled directly into the capsule without further downstream processing. This generates new possibilities for oral delivery for new classes of APIs and could enable faster to human clinical development because the drug alone can be tested using the Enprotect capsule without formulation studies to evaluate the need for an enteric dosage form.

DYNAPRO ZETASTAR

A nanoparticle analysis instrument with three scattering light techniques

Waters Corporation

Developing LNPs that are both effective and safe requires light scattering techniques to deliver essential and reliable nanoparticle measurements. The DynaPro ZetaStar combines three light scattering techniques in a single device, including Fiber Interferometric Doppler Electrophoresis by Light Scattering (FIDELIS). Unlike conventional light scattering analysis, FIDELIS operates at kHz frequencies to eliminate noise from mechanical disturbances, delivering increased sensitivity and faster measurements (up to tenfold). The system also uses automated data quality assessments and data capture to enable precise characterization of particle size.

Waters hopes that DynaPro ZetaStar's ability to characterize particle size by simultaneously conducting dynamic light scattering and electrophoretic light scattering measurements could lead to the development of more stable drug formulations, drug delivery, and enhanced bioavailability. The heightened sensitivity also ensures the detection and characterization of trace substances, enhancing drug safety.

EZ BIOPACZIP

Closed loop powder transfer to minimize the risk of exposure and contamination

ILC Dover

ILC Dover's EZ BioPacZip is a contained powder handling and transfer technology suitable for buffer and media preparation that builds on the company's EZ BioPac line. The product, developed through a partnership with Rommelag Flex, creates a fully closed loop to eliminate cross-contamination and operator exposure risks, avoid shedding issues and seal holds, and is designed to be anti-static and anti-dissipative to prevent powder retention.

There is an upper zipper attached to the EZ BioPac, which is single use, and a lower zipper with a canister – a reusable component. When zipped together, the system forms a closed barrier for powder transfer. According to ILC Dover, the zipper overcomes the complexities of using valves, which can be challenging to open and close. Multiple volumes and flange sizes are available, as well as a non-gamma-irradiated and gamma-irradiated version. Custom versions are also available.

FORMsightAI

Cell and gene therapy development through AI and machine learning

Form Bio

FORMsightAI uses AI and machine learning (trained on multiple public and proprietary nucleic acid-based datasets) to help cell and gene developers model billions of potential construct candidates in a swift and safe method. Most cell and gene constructs can be shaped by design choices for 8–10 different key elements beyond the therapeutic gene of interest, so fully exploring the totality of possible vector designs requires the analysis of billions of candidates. Form Bio's solution delivers the computational capabilities to explore and model the broadest range of vector designs, helping companies to create programs that significantly shorten the critical development stage between early discovery and preclinical regulatory filings. The technology features capabilities for drug product characterization, multi-candidate comparison, bioreactor simulation, gene expression prediction, and immunotoxicity analysis, as well as AI-powered candidate optimization.

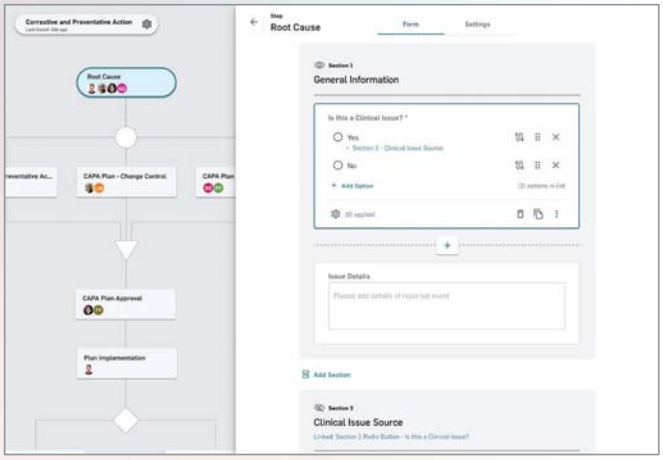
INFINITY MTx

Microfluidic chips for enhanced cell yield and seamless scalability in cell therapy manufacturing

CellFE

Cellular engineering is a critical step in cell therapy, but existing approaches can have limitations. Viral techniques, though dominant, face issues, including high costs, restricted editing capabilities, regulatory obstacles, and safety concerns. On the other hand, non-viral approaches include electroporation – a long-standing method with a number of downsides, including diminished cell health, low yield of edited cells due to its harsh nature, and scalability challenges that delay patient treatment. CellFE's Infinity MTx intends to overcome these hurdles.

Infinity MTx is a microfluidic cell engineering platform that performs rapid gene editing through streamlined workflows, whilst ensuring gentle cell treatment, rapid cell recovery, and high yields of healthy cells. This is achieved by leveraging the inherent biomechanical properties of cells, adapting rapidly to their in vivo environment. As cells flow through microfluidic channels at high speeds, they briefly compress while passing under a single ridge. This compression results in a transient reduction in cell size. Within milliseconds of re-expansion, the payload is actively transported into the cell. The design of the microfluidic chip allows for scalability and greater cost efficiencies in cell therapy development and manufacturing.



MASTERCONTROL ADVANCED QUALITY EVENT MANAGEMENT

No-code process quality event management software

MasterControl

MasterControl's advanced quality event management software is a cloud-native, no-code solution that enables life science quality managers to own and iterate their quality process. Through its combination of highly flexible digital solution and analytics, alongside its no-code functionality, the software allows users to easily modify workflows as processes or regulations change. The software also features automated validation testing with patented "Validation on Demand," helping to improve compliance with regulatory standards.

MasterControl claims that the technology delivers on the promises of "Quality 4.0" initiatives. Quality managers can use the software's AI capabilities to analyze massive amounts of data to make proactive process improvement decisions. For example, quality managers will be able to access data to improve workflow routing, conduct root cause analysis, and suggest the best mitigation actions. Additionally, quality managers can apply dynamic workflow routing: as certain data is entered, workflows are set based on the conditions.

According to MasterControl, there is currently no other process management tool in the market that uses no-code technology and is purpose-built for the specific needs of life sciences manufacturing.

OPENTRONS FLEX

Accessible and user-friendly liquid-handling AI-driven lab robot

Opentrons Labworks

The Opentrons Flex is an accessible, user-friendly lab robot designed to accelerate bioautomation and empower scientists to efficiently process multiple samples simultaneously and at a larger scale. The system is built using genomics and proteomics workflows, allowing researchers to automate a wide range of tasks, such as next generation sequencing library preparation, PCR, protein purification, nucleic acid extraction, and precise aliquoting. The vision: to make advanced lab automation more accessible, liberating scientists from the bench and allowing them to focus on the complex challenges in science.

Through the digitization of manual laboratory processes, researchers can now automate a wide range of benchside tasks, ensuring precision and reducing time and costs compared with traditional methods.

According to the developers, the total cost of ownership is just 10 percent that of its competitors. The company also claims that it is the first liquid-handling robot designed to be compatible with "design-of-experiment" programs, including AI-driven agents using large language models.

ORBITRAP ASTRAL MASS SPECTROMETER

Designed to generate two times deeper proteome coverage and four times more throughput

Thermo Fisher Scientific

Thermo Fisher Scientific claims that the Orbitrap Astral Mass Spectrometer is "one of the most significant advancements in mass spectrometry in 15 years." The instrument provides up to two times deeper proteome coverage and four times higher throughput compared with current mass spectrometers. It can be used to uncover insights in biology and disease mechanisms from various applications, including single-cell proteomics, quantitative proteomics, and translational proteomics.

The system combines three mass analyzers: a quadrupole mass analyzer for high selectivity and high ion transmission, an Orbitrap mass analyzer for high dynamic range and high-resolution measurements, and the new Astral analyzer for fast and sensitive measurements. The Orbitrap Astral MS expands the scope and statistical power of proteome analysis by analyzing over a million protein groups across 180 samples in a day, measuring more than 8,000 protein groups in each sample, allowing for the discovery of meaningful biological insights with accurate and precise quantities over a larger range. In addition, the system allows high-resolution data-independent and data-dependent acquisition, as well as tandem mass tag-based multiplexed quantification.

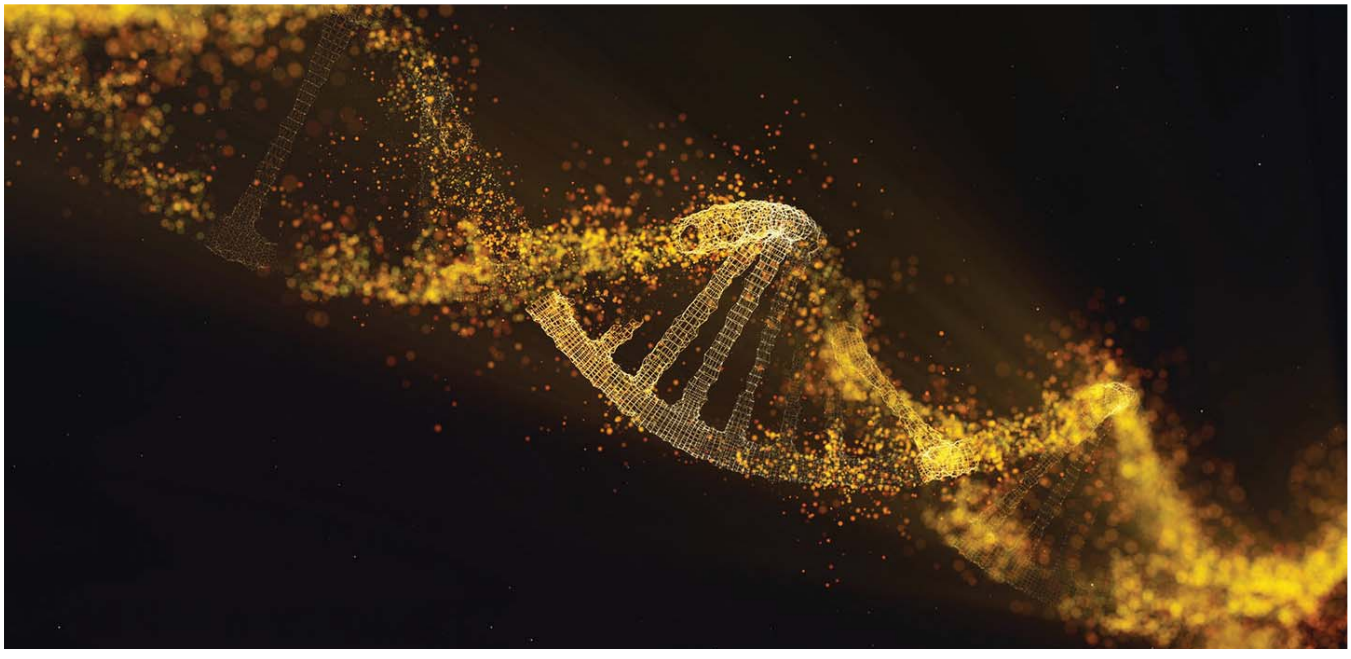
PIN-POINT BASE EDITING REAGENTS

Reagents to improve access to gene editing

Revvity

Broadening access to base editing was Revvity's goal when releasing its range of Pin-Point base editing reagents. The reagents can be used in-house across a range of research areas to facilitate genomic insights and cellular therapy research, and includes mRNAs for nCas9 and rat APOBEC, as well as three control guide RNAs designed for knocking out the TRAC, CD52, and PDCD1 loci. Revvity has demonstrated the performance of the reagents in T-cells and pluripotent stem cells.

Pin-Point is one of the few base editing technologies already used in clinical settings, allowing researchers to perform efficient, customizable and off-the-shelf precision nucleotide conversions for single and multiplex gene editing applications. Until now, Revvity claims that base editing reagents were either custom-ordered by end-users or obtained by non-profit laboratories as individual components. The new reagents mean that users can evaluate the Pin-point base editing platform in-house.



PROTEOSUITE ORAL

A toolkit to assess the developability of targeted protein degraders

Catalent

Targeted protein degraders (TPD) could "revolutionize" the field of small molecules, according to Catalent. However, the complex structures and physicochemical properties of TPDs makes satisfactory oral exposure challenging. They also present additional formulation and handling challenges compared with conventional small molecules. Catalent's ProteoSuite Oral toolkit helps assess the developability of protein degraders, including oral bioavailability. The assessment can be performed even with limited quantities of API, and draws on a range of specialized capabilities to thoroughly evaluate candidate molecules. By providing insight into formulation strategy, the toolkit helps streamline the journey from laboratory development, to clinical application, and beyond. The toolkit builds upon Catalent's expertise with multitudinous protein degrader programs, while tapping into TPD-specific developability models that scrutinize the physicochemical properties and molecular descriptors of these unique compounds.

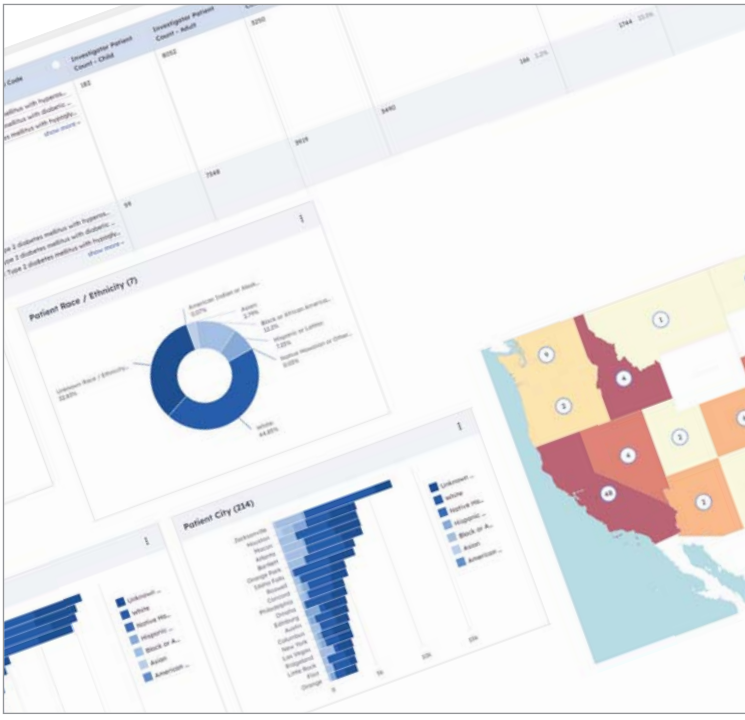
RoSS.PADL

Standardized homogeneity and cooling in the aliquoting of pharmaceuticals

Single Use Support

Managing the aliquotation of liquid drugs poses significant challenges because of the diverse viscosities, degrees of sedimentation, and other unique properties inherent to different pharmaceutical liquids. In the case of cell-based suspensions, antibody-drug conjugates, bacterial fermentations, and other similar substances, the lack of homogeneity can result in inconsistent (cell) counts, particle distribution, and active ingredient concentrations within aliquoted single-use containers.

Traditionally, homogenization was a manual process, carrying inherent risks, such as breakages in single-use systems leading to potential contamination, inconsistent filling of bags with varying volumes and sediment concentrations, and unintentional heating of fluids due to manual handling. The RoSS.PADL platform helps ensure standardized homogeneity and cooling in the aliquoting of biopharmaceutical liquids. A kneading mechanism ensures homogenization, facilitating consistent cell counts throughout the filling process into single-use bags. Simultaneously, a cooling element expedites the process while maintaining precise temperature control to prevent reduction in cell viability.



SITETROVE DIVERSITY MODULE

Identifying investigators with clinically relevant/demographically diverse patients

Citeline

Citeline's Sitetrove Diversity Module helps with early clinical trial planning, including feasibility and site selection, enabling sponsors and CROs to identify and engage with suitable investigators. At the individual investigator level, the module offers assessments of total unique patient counts, further dissected by race, age, and gender demographics across more than 3,000 diseases, including rare indications. Additionally, Citeline's accompanying Diversity API allows clients to integrate diversity insights into internal workflows and proprietary metrics for more informed decision-making.

A common goal in the drug development industry is greater patient diversity in clinical trials. It is important to ensure that underrepresented populations are given every opportunity to participate in research and to feel comfortable doing so. Greater diversity in clinical trials leads to better safety, efficacy, and ensures the advancement of life-saving medicines.

VERTIVA

A pre-filled and pre-loaded on-body delivery system

Stevanato Group

According to Stevanato, Vertiva helps improve treatment adherence by providing an enhanced patient experience. The on-body delivery system uses a single-use pod with a prefilled and preloaded 3 mL ISO cartridge, and is suitable for a range of subcutaneous therapies. The system also incorporates a smart, reusable controller that can be pre-programmed to deliver micro-precision basal doses and full-content bolus injections. It can also accommodate different types of primary packaging for larger injection volumes, delivery duration, and user interface. As the controller can be reused, it can help reduce its environmental impact.

The name of the device is taken from the word "versatility" – and Stevanato hopes it will support pharma companies to increase the accessibility of in-home treatment options. Connectivity options also mean that Vertiva is ready for digital health applications.

DIVE DEEP

INTO THE MOST COMPLETE FAMILY
OF WASHING MACHINES.

Efficiency. Flexibility. Performance.

From the depths of our experience, knowledge of water
and understanding of your needs,
comes the most extensive range of washing solutions.

the All-In-One **PHARMA**
ima.it/pharma

IMA ACTIVE
Solid Dose Solutions

the Medicine Maker

The INNOVATORS

Continuous PROGRESS

Two more innovative technologies helping to make pharmaceuticals manufacturing smarter, safer, and more sustainable

NANOASSEMBLR™ COMMERCIAL FORMULATION SYSTEM

Automated, single-use system from Precision NanoSystems for clinical and commercial production of lipid nanoparticles

The NanoAssemblr™ commercial formulation system is an automated, single-use system for the clinical and commercial production of lipid nanoparticles (LNPs). The system simplifies GMP manufacturing while addressing the unique challenges of genomic medicine development through an automated workflow that guides the user through the process of priming, calibration, formulation, and in-line dilution. Intuitive software enables 21 CFR Part 11 compliance and electronic batch records capture real-time reporting of flow rate and pump speed.

The commercial formulation system builds on the innovative NxGen™ technology that minimizes process development during scale-up to commercial manufacture while providing precise control of mixing parameters. Its single-use flow path minimizes the need for sanitizing and performing cleaning validation, enabling efficient changeover between production runs, minimizing the risk of cross-contamination, and supporting multi-product manufacturing.

Considering the number of variables throughout the production workflow, flexible and robust technologies will be key to expanding LNP drug development to new therapeutic targets. The NanoAssemblr commercial formulation system standardizes workflows, increases operational flexibility, and reduces process development, accelerating time to market of RNA vaccines and therapeutics.

More information:
www.precisionnanosystems.com

UPPING THE GAME IN SOFTGEL QUALITY

Softgel capsules offer many patient benefits as a delivery format, including ease of swallowing and good bioavailability, but for manufacturers, producing a quality product is not at all straightforward

Advances in APIs have not made the situation any easier, with many compounds known to interact with ingredients in the shell and to cause issues with capsule stability. For instance, surface-active compounds like phospholipids and components used in self-(nano)-emulsifying drug delivery systems (SEDDS/SNEDDS) tend to inhibit capsules seam formation. Poor seam formation can then cause capsule contents to leak, either during production, packaging or storage, with substantial negative consequences.

Why are leakers a problem?

Leaking capsules (leakers) can cause multiple problems, including waste of ingredients, damage to additional capsule coatings, contamination of surrounding capsules and production areas, and the need for downtime and cleaning. For patients, leakers can mean they don't receive the correct API dose and they may experience unpleasant tastes or irritation of oral mucosa. In the worst-case scenario, leakers can lead to expensive product recalls.

Traditionally, if leakers do occur during pharmaceutical production, manufacturers have to laboriously clean every capsule in the batch (i.e. by passing them through an ethanol bath to strictly rule out the possibility that residual API remain on their surfaces). All occurrences of leaks must be carefully recorded and records meticulously kept.

Unfortunately, a survey undertaken recently by leading gelatin supplier GELITA has confirmed that leakers have, until now, been a universal issue.

What the survey found

GELITA surveyed major softgel players around the world and found that all of them experienced leakers. While the producers did all they could to maintain capsule integrity, including modifying production parameters such as temperature settings in the machine and machine speed, they all said that leakers were unavoidable. Indeed, more than half were prepared to put up with around 5 percent leakers as an inevitable part of production.

Believing that 5 percent leakage was 5 percent too much, GELITA has worked on developing a solution – a new type of gelatin called EASYSEAL® that has been proven to deliver more reliable softgels of superior quality with a vastly reduced chance of leaking.

A game changer

Gelatin dominates the market as the preferred excipient for softgel shells, thanks to its unmatched advantages over other options. However, not all gelatins are equal, and EASYSEAL® has been shown in lab trials at the University of Heidelberg as well as during industrial production to eliminate or vastly reduce the likelihood of leakers.

"EASYSEAL® outshines other gelatins with its exceptional qualities, ensuring more dependable capsule sealing," says Dr. Ulrich Mach, Application Technology & Product Development at GELITA. "Furthermore, EASYSEAL® is compatible with ingredients that typically cause filling challenges."

What is EASYSEAL® ?

EASYSEAL® is a natural, pharmaceutical grade gelatin. It tolerates equipment temperature changes during production and is suitable for any type of fill, including Rx, OTC and herbal medicines, as well as food supplements such as vitamins, minerals, and fish oils. Its special properties enable trouble-free filling of traditionally difficult to handle or surface-active fill components, including SEDDS and SNEDDS.

EASYSEAL® has been shown to increase capsule seam thickness by at least 50 percent, delivering robust capsules even at high production speeds. It also makes capsules less likely to leak during drying, as well as cutting time required for drying by as much as 50 per cent. This enhances production capacity and cuts energy requirements. Standard gelatin does not perform nearly as consistently under temperature fluctuation as EASYSEAL® does – due to the very exceptional production process.

"Overall, EASYSEAL® has been shown to boost production efficiency significantly, thanks to reduced waste, shorter drying times and better yield," says Mach. "It reduces the incidence of leakers, generating substantial cost savings and improved production efficiency. Ultimately, this new type of gelatin delivers a superior end product for the pharmaceutical industry and for patients."

EASYSEAL® is available in bovine and porcine forms and is produced in line with FDA regulations, HACCP, ISO9001:2015 and FSSC22000. A China DMF (Drug Master File) is also available to ease entry into the Chinese market.

More information, including full technical specifications, is available in the downloadable e-book on the GELITA website www.Gelita.com

eppendorf

From a scientific concept to the development of novel therapies

The **Eppendorf Bioprocess Unit** builds on decades of experience in upstream bioprocessing; since more than ten years Eppendorf is committed to contribute to the advancement of stem cell cultivation in stirred-tank bioreactors. The scalability, robustness, quality, and cost-effectiveness of cell culture processes are key to success when translating basic research to the development of commercially viable cell and gene therapies. Eppendorf supports you in developing powerful upstream bioprocesses for cell and gene therapy development.

Visit our website to learn more about how we can support you!

Become a bioprocessing expert!
Join us at https://eppendorf.group/bioprocess-cgt-solutions

www.eppendorf.com/bioprocess

Credit: Shutterstock

Core Topic
Cell & Gene

AZ boost. AstraZeneca has partnered with Cellectis to advance next-generation therapies in various areas, including oncology, immunology, and rare diseases. Under the agreement, AstraZeneca will gain access to Cellectis' gene editing technologies and manufacturing capabilities for the development of novel cell and gene therapy products. The collaboration has exclusively reserved 25 genetic targets for AstraZeneca, with the potential for up to 10 candidate products.

DREAM big. Rice University bioengineers have formulated a tool that activates silent or insufficiently expressed genes using human-derived proteins, allowing our cells to turn on specific genes in response to mechanical cues. Coined CRISPR-DREAM (short for CRISPR-dCas9 recruited enhanced activation module), the tool is said to be a smaller and more effective version than their alternative counterparts when controlling gene expression. The researchers theorize that DREAM could enable better and safer gene and cell therapies, as well as more accurate disease models to address haploinsufficiency disorders, which cause a number of hard-to-treat conditions, including epilepsy, some cancers, and immunodeficiency.

Gel the wound. Researchers from the National University of Singapore have engineered a first-of-its-kind "mechano-activated cell therapy" that can heal diabetic wounds, reduce recurrence rates, and lower the incidents of limb amputations. A study (DOI: 10.1002/adma.202304638) showed the treatment, coupled with magnetic stimulation, healed diabetic wounds roughly three times faster than conventional approaches. "Our technology addresses multiple critical factors associated with diabetic wounds, simultaneously managing elevated glucose levels in the wound area, activating dormant skin cells near the wound, restoring damaged blood vessels, and repairing the disrupted vascular network within the wound," said Andy Tay, Assistant Professor at NUS College of Design and Engineering as well as the NUS Institute for Health Innovation and Technology.

Epic Bio flies high with Kite. Kite and Epicrispr Biotechnologies (Epic Bio) have agreed a research collaboration and license partnership to use Epic Bio's proprietary gene regulation platform to develop cell therapies for cancer. The agreement will allow Kite to leverage the licensed technology to modulate certain genes to potentially enhance CAR T-cell functionality. "Cell-based cancer immunotherapies have reshaped modern cancer care, but we have still only scratched the surface of their potential benefit for patients. At Kite, we are committed to developing next generation CAR T-cell therapies with the goal of reaching more patients with cancer who could benefit," said David Barrett, Vice President of Cell Biology and Translational Medicine at Kite, in a statement.

IN OTHER NEWS

Chimeric Therapeutics receives FDA clearance for IND application of CHM 2101 CAR T cell therapy targeting advanced gastrointestinal cancers

Regeneron reports promising phase I/II CHORD trial results for otoferlin gene therapy in children with genetic hearing loss

Bit.bio launches CRISPR-Ready Cells range designed for scientists looking to generate gene knockouts in physiologically relevant human cells

Landmark Bio signs multi-year strategic manufacturing agreement with Galapagos for development of CAR-T cell therapy clinical programs focused on oncology

Goodroot and its affiliate companies release guide on financial implications of gene therapies titled "Cost vs Cure: Gene Therapy's Financial Blueprint"

Uniting a Cell and Gene Kingdom

Exploring the ins and outs of a recent UK-based collaboration between two prominent advanced medicine players

By Jamie Irvine

The UK currently holds the crown for the highest concentration of cell and gene therapy companies in Europe – a significant portion of which are situated in Stevenage, including the Cell and Gene Therapy Catapult (CGT Catapult). To further bolster the UK's capabilities in the cell and gene sector, the CGT Catapult has announced a partnership with Cryoport to establish the country's first global supply chain logistics center.

Members of the Cryoport UK team have maintained a longstanding connection with Catapult's leadership since their formation in 2012. Discussions around their potential collaboration commenced in 2021 – but it wasn't until 2023 that an opportunity emerged to secure a facility adjacent to Catapult's UK Manufacturing Innovation Centre in Stevenage.

The new facility – and the new partnership – has several key objectives. "We will focus on optimizing just-in-time logistics, simplifying UK import and release procedures, and implementing digital supply chain enhancements," said Robert Jones, Vice President of Global BioServices at Cryoport Systems. "This, in turn, should hopefully accelerate the development and commercialization of cell and gene therapies in the UK. We also hope the proximal location of Cryoport will provide immediate logistics support to Catapult's many therapy developer collaborators as well as other cell and gene therapy companies in the immediate area."

The Cryoport GMP-compliant facility is equipped with liquid nitrogen, back-up power systems, stringent security measures, and high-quality HVAC, enabling rapid operations with minimal infrastructure modifications and offering modernized solutions. The goal is to reduce risks and costs while capitalizing on the UK's favorable clinical ecosystem and well-funded advanced therapy programs, positioning the country as

"Today, companies use a diverse array of systems and technologies, making harmonization a herculean challenge."

a global hub for manufacturing and clinical research.

According to Mark Sawicki, President and CEO of Cryoport Systems and Chief Scientific Officer of Cryoport, standardization will also be important to help grow the UK's cell and gene sector.

"The current obstacle we face as an industry is the absence of standardization, a practice vital for ensuring consistent quality, regulatory compliance, and interoperability among stakeholders. Today, companies use a diverse array of systems and technologies, making harmonization a herculean challenge," says Sawicki. "And though achieving comprehensive standardization across all facets of the cell and gene therapy industry may be a stretch too far for now, it's essential to consider shorter-term solutions as well. By introducing and gradually expanding standardization efforts, even within specific sectors of the field, the cell and gene space will benefit immensely."

Operations are set to commence early 2024.

Improving AAV Production

How a three-way collaboration aims to use digital twins to refine the efficiency of adeno-associated virus manufacture

Statistics suggest that over 65 percent of gene therapies in development use adeno-associated virus (AAV). However, AAV production is complex and time consuming, partly because current analytical methods mainly rely on manual sampling. Now, the Cell and Gene Therapy Catapult (CGT Catapult), in collaboration with Rentschler Biopharma and Refeyn, is hoping to change things. Here, Yatindra Tirunagari, Technical Expert at Rentschler Biopharma discusses the nature of the partnership – and what it could mean for the future of AAV manufacturing.

What sparked the collaboration?

Our mutual understanding of the challenges we face as an industry was a monumental factor!

And what is the main focus?

Ultimately, we aim to develop and apply process analytical technologies to improve AAV manufacture. Real-time monitoring and feedback control for AAV manufacturing would allow real-time decision-making, reduce processing bottlenecks, and enhance process reproducibility and batch-to-batch comparability.

To get there, the teams will carry out high throughput and automated sampling and analysis of AAV material throughout the production process. This data will then be leveraged for the creation of digital twins: digital models of the manufacturing process that can be used to further refine and improve the efficiency of the process.

Afterwards, we hope to use these digital models to perform initial tests of changes to the process in a digital environment, which should reduce the number of expensive and time-consuming physical tests which need to be carried out in the laboratory. This will allow us to assess for improvements in productivity and AAV yield using automated analytical technologies. For example, we can use Refeyn's technology to assess the proportion of full AAV capsids produced. This is a key measurement for the industry, as quantity of full AAV capsids indicates process efficiency but may also impact clinical efficacy.

What are the current limitations of AAV manufacture?

The optimization of upstream and downstream processes depends on the ability to rapidly characterize critical quality attributes (CQAs). In the context of rAAV production, the virus titer, capsid content, and aggregation are identified as potential CQAs, affecting the potency, purity, and safety of rAAV-mediated gene therapy products.

Analytical methods to measure these attributes commonly suffer from long turnaround times or low throughput for process development – partly because current analytical methods mainly rely on manual sampling. However, rapid, high-throughput methods are beginning to be developed and commercialized; as is also the case in the collaboration project between Rentschler Biopharma, CGT Catapult and Refeyn. These methods are not yet established in academic or industrial practice, and supportive data are scarce.

We believe active engagement across scientific disciplines (academia, industry experts and technology vendors or suppliers) will allow us to openly discuss the challenges we face, whilst creating an environment to discover solutions.

Refeyn's technology is a key part of the partnership; why is this technique so promising?

Current standard practices involve analytical ultracentrifugation, electron microscopy or PCR/ELISA – each of which present drawbacks (not least long turnaround times, high sample consumption, and the need for specialized staff).

Mass photometry is a bioanalytical technique that measures the mass of AAVs in solution and at a single particle level. The analysis requires smaller amounts of sample than other techniques and takes less than five minutes. In our collaboration, Refeyn's technology will be used to assess the proportion of full AAV capsids produced. This is a key measurement for the industry, as the quantity of full AAV capsids indicates process efficiency but may also impact clinical efficacy.

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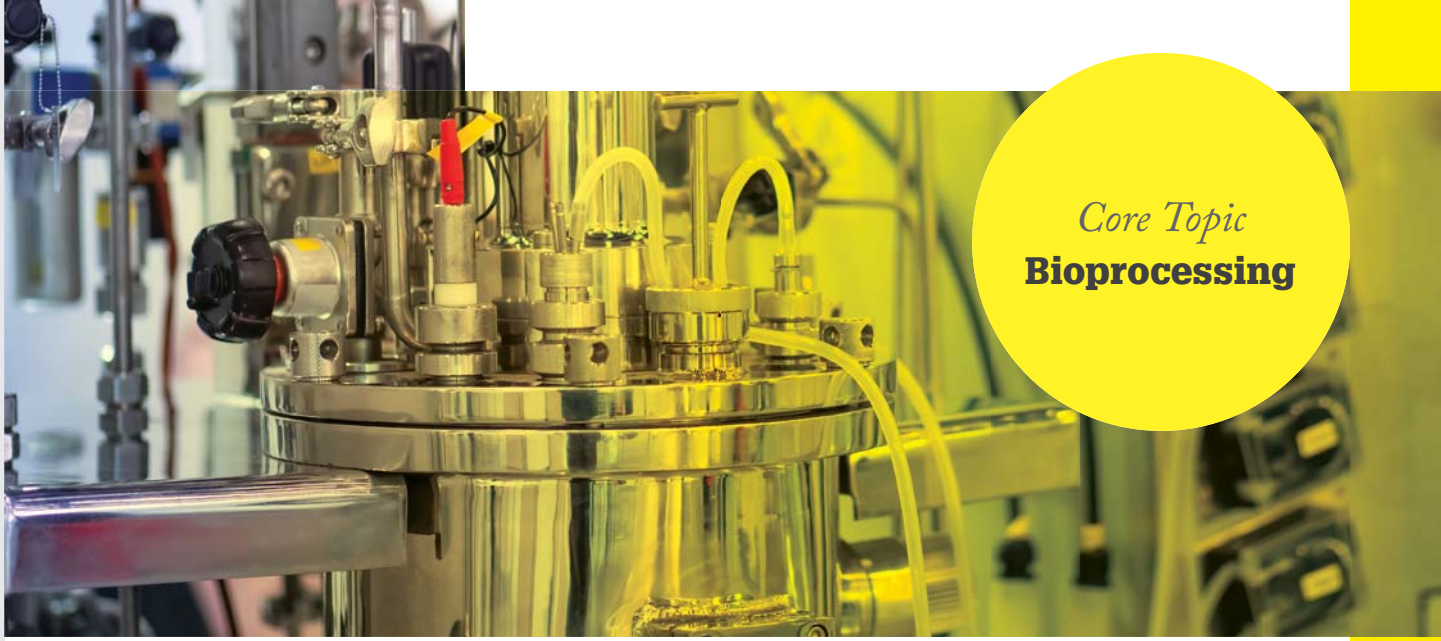

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Core Topic
Bioprocessing

Not renewed. The EMA's CHMP committee has recommended not renewing the conditional marketing authorization for GSK's multiple myeloma drug Blenrep (belantamab mafodotin). The drug received conditional approval in August 2020, but a specific requirement of the authorization was for GSK to conduct a study comparing Blenrep to pomalidomide plus low-dose dexamethasone. After reviewing data from the recent DREAMM-3 study, the committee could not confirm effectiveness. The drug was pulled from the US market in 2022.

Vaccine prizes. Luminary Labs has partnered with the Biomedical Advanced Research and Development Authority to launch two competitions designed to promote innovation in vaccine technologies. The first, due for launch in 2024, will focus on "catalyzing the development of patch-based vaccine delivery technologies." Up to $50 million will be available in prizes. The second will launch in 2026, with a focus on "reducing the number of doses needed to achieve an effective immune response against a novel coronavirus or pandemic influenza," and will have up to $41 million available as prizes.

Save water. Peter Satzer from the Institute of Bioprocess Science and Engineering in Vienna, Austria, has published an article demonstrating a risk-based assessment for buffer recycling that can quantify potential savings in water-for-injection (doi: 10.1016/j.bej.2023.109140). With sustainability being a key topic for the biopharma industry, water use, such as water for injection, is under scrutiny. Some strategies have suggested that recycling buffers can lead to savings of 90 percent, but Satzer shows that only around 14 percent is achievable with simple solutions, rising to around 23 percent if cross-batch recycling is used. Satzer writes, "Past estimated or hopes of savings of 70, 80 or even 90% where [sic]too optimistic and did not take risk to the product or practical considerations."

Ultra intensification. WuXi is launching a proprietary bioprocessing platform called WuXiUI, which the company describes as an "ultra-intensified, fed-batch solution that enhances the productivity and quality of multiple different CHO or other mammalian cell lines and product modalities." The platform uses an intensified intermittent-perfusion fed-batch approach upstream to achieve an increase in productivity of around 3–6 fold in a typical fed-batch 14 day culture. For example, the company says it achieved titers of 25 g/L in 14 days for a bispecific antibody. WuXi also adds that the technology can reduce drug substance manufacturing COGS by 60-80 percent compared to fed-batch processes in single-use bioreactors.

IN OTHER NEWS

Altaviz launches auto-injector AltaVISC for delivery of high viscosity and high-volume biologics; device uses compressed gas cylinders called Pico-Cylinders

Thermo Fisher Scientific expands manufacturing capacity at St Louis site in Missouri, US, to support complex biologics

Moderna and CEPI partner to use mRNA platform to develop "vaccines against viral disease outbreaks that threaten global health" in line with CEPI's "100 Days Mission"

ATCC and the US Pharmacopeia launch joint set of products that can be used for measuring residual host cell DNA in biotherapeutics

Vaxcyte and Lonza expand collaboration for manufacturing pneumococcal conjugate vaccines

Cell Culture Media Is Big Business

Merck's Darren Verlenden discusses the strategy and ethics behind the expansion plan in Lenexa, Kansas

As Head of Process Solutions for the Life Science business sector at Merck, Darren Verlenden drives differentiated product and process innovations. With nearly 30 years of experience in the industry, he has come face to face with the challenges that come when bringing bold and creative therapies to market. When we heard about the €23 million investment into Merck's cell culture media plant in Kansas, we wanted Verlenden to explain the reasoning.

What's the strategy behind the expansion?

Global demand for bioproduction and associated process solutions is increasing. And cell culture media is an essential raw material used in the manufacture of life-saving therapies. Because of its central role in biomanufacturing, a consistent supply of high-quality media is required to deliver the necessary concentration and protein quality for therapeutics. In short, we expect to see strong growth here. The expansion is also in line with our strategy to expand and regionalize our manufacturing network.

With the expansion, Lenexa becomes our largest dry powder cell culture media facility and Center of Excellence in North America. By adding 9,100 square meters of lab space and production capability to manufacture cell culture media, the investment reflects our strategy to expand and diversify our supply chain to ensure we meet current and future demand for cell culture media.

We now have three centers of excellence for dry powder cell culture media manufacturing across the globe. Our site in Nantong, China, serves the Asia Pacific region, and another site in Irvine, Scotland, serves the Europe, Middle East and Africa regions.

How does the company plan to use digitalization and Industry 4.0 to improve manufacturing capacity?

We already see a great deal of value that digitalization and industry 4.0 can bring in as we aim to speed up processes and gain better transparency for all stakeholders involved. For example, we are working on developing a digital platform that will leverage capabilities around data mining and artificial intelligence to enhance our cell culture formulation offerings and single chemical ingredients in terms of quality and performance.

We have also developed a program, named eMERGE, which is optimized to proactively exchange eData with our customers and enhance their knowledge management approach without ever requiring them to leave their established data ecosystem. I'd say it's poised to digitally transform logistical and analytical processes.

Furthermore, we have developed an in-line Raman analyzer that enables customers to implement automated process control from media preparation to cell culture expansion as they move towards Industry 4.0. The Raman PAT platform can monitor USP performance attributes in real-time, empowering process optimization and streamlining quality assurance to enhance manufacturing capacity and efficiency.

In what ways does the expansion contribute to the achievement of Merck's sustainability goals?

Our life science business is aiming for climate neutrality by 2040. As of 2022, we have already achieved a 33 percent absolute reduction in scope 1 and 2 emissions globally compared with our 2020 baseline – and all our sites in the US are already matched with 100 percent renewable electricity. With this expansion, we had the opportunity to upgrade multiple pieces of equipment to improve energy and water efficiency.

Water stewardship and conservation is of key importance to us, and our life science business goal is to reduce our water intensity score by 10 percent. We replaced a continuously operating purified water generation system to one that works on-demand. We updated our older roof with a white thermoplastic polyolefin membrane roof, which has sun-reflective properties. As part of upgrading the roof, we also replaced five rooftop air conditioning units that used ozone-depleting R22 refrigerants with units that use non-ozone depleting 134A-refrigerant. Other upgrades included in the Lenexa expansion were replacing an older chiller with a more energy efficient model, and upgrades to our compressed air systems.

Expanding the footprint of our operations is a necessary move to improve the products and services we provide to our customers and their patients around the world. But we are acutely aware of the impact these expansions could have on the environment. Addressing and improving our sustainability and environmental policies is a responsibility I, and the teams I lead, take very personally, seriously, and proactively.

Putting the "Go" in Oligonucleotide Manufacturing

How machine learning is set to change the oligonucleotide manufacturing landscape

By Ben Pellegrini, CEO and Co-Founder of Intellegens

With the aim to overcome key barriers to applying machine learning (ML) to real experiments and processes – for example, the fact that ML typically struggles with 'sparse' data (data with gaps) – our latest project, in partnership with the Centre for Process Innovation (CPI) and with funding from Innovate UK, focuses on the potential for ML to act as a catalyst for manufacturing oligonucleotide therapeutics. We are improving predictive modelling tools, experimental program design, optimal process parameter discovery, and target output identification.

Oligonucleotides are difficult to manufacture – particularly at scale. They are large, complex molecules that require a multi-stage synthetic process, interleaved with significant purification and analysis stages. The presence of impurities or small variations in reaction conditions and process steps can make significant differences to the structure, yield, and quality of the end product. Synthesis is expensive, meaning that experimental data is often sparse, and research teams would prefer to extract as much value as they can from the data that exists. Alongside these common industry problems, oligonucleotide manufacturing also has significant sustainability challenges; namely, large amounts of waste produced, poor atom economy, and low use of renewable feedstocks.

For these reasons, oligonucleotide manufacturing is an ideal target for ML, which can help detect subtle, non-linear relationships in multi-parameter data that might otherwise be missed. I expect ML to help research teams better understand the key factors driving oligonucleotide manufacturing processes, leading to improved design and control of these processes.

The importance of oligonucleotide therapies cannot be understated. Despite significant advances in medicine, there is still a large gap between the number of diseases and disorders that are druggable with approved therapies. Oligonucleotide therapies represent a relatively new and innovative approach with the potential to treat a wide range of diseases, including rare genetic disorders, certain types of cancer, and neurodegenerative conditions. The high specificity of oligonucleotides – and their ability to target gene mutations or protein expression – means that they are a form of personalized medicine, with fewer off-target effects and, potentially, fewer side effects than small molecules. Given the promise, many companies within the pharma industry are either investing heavily in platform R&D to progress oligonucleotide pipelines or forming partnerships and collaborations to advance these to commercialization. Going back to ML adoption in this space, oligonucleotides will likely suffer the same challenges seen in other modalities and sectors. Traditional ML methods and algorithms require large, high-quality datasets for training. And as noted, In oligonucleotide manufacturing it is challenging to obtaining sufficient data – especially for highly complex and nonlinear proprietary processes. Over-simplified models may not provide meaningful insights. Building models that can generalize across different data formats and processes for different pharma companies will also be challenging. As will the integration of ML solutions into existing manufacturing systems, where it is important to work seamlessly with automation and control systems. The final barriers to adoption are simply inertia or a lack of knowledge and understanding of ML technologies.

Certainly, a small number of specialist companies have made progress in addressing the manufacturing challenges of oligonucleotides, but their insights and models are often proprietary (and pharma is an industry where knowledge is not widely shared). As with many challenges, collaboration is likely key; pre-competitive projects could combine expertise, with ML models acting as a vehicle for capturing and sharing knowledge among the collaborating organizations. This way, what is learnt can be shared to accelerate progress and drive innovation.

And in my view, it's absolutely worth it! A somewhat consistent rule of thumb for ML technology when applied to the DoE is a reduction of around 50–80 percent in the number of experiments required to achieve a given objective. Furthermore, it could generate new insights and guide informed decision making. Yes, it's speculative – but the effective use of ML could drive two- to five-fold reductions in the problematic process development phase of bringing new oligonucleotides to market.

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Core Topic

Small Molecule Manufacture

Get your coat on. Mini-tablets and pellets made into hard capsules or administered using special dosing units offer advantages in multiparticulate drug delivery systems and are suitable for controlled drug release using polymer coatings, according to a study by the Anhalt University of Applied Sciences, Germany, and IMA (DOI: 10.3390/coatings13111891). Four kinds of solid drug preparations were manufactured with inert pellets coated with sodium benzoate and, in a second step, with ethylcellulose. The sodium benzoate release plots showed a retarded release which increases with increased ethylcellulose layer thickness. The different formulations of coated pellets, mini-tablets, and normal tablets offer variable drug release kinetics depending on the biopharmaceutical and pharmacological requirements.

Blue is the color. Opioid antagonist naloxone has the potential to save lives by reversing the effects of an opioid overdose if available at the right time, according to Daniel Kohane of the Boston Children's Hospital. His research team is looking into ways to make the medication more accessible even before it's needed. A proof-of-concept paper has been published in Nano Letters (DOI: 10.1021/acs.nanolett.3c03426) showing how Kohane's research team has designed injectable nanoparticles that release naloxone when triggered by blue light. Described as "on-demand phototriggered opioid reversal," the nanoparticles released the antagonist and successfully reversed the effect of morphine in mice.

The only way is Yup. Viatris and Theravance Biopharma have announced positive results from the China-based phase III placebo-controlled clinical trial of Yupelri (revefenacin), a nebulized muscarinic antagonist for treating COPD. Yupelri met its primary efficacy endpoint by demonstrating an increase in trough FEV1 (forced expiratory volume in one second) versus placebo. Viatris president Rajiv Malik said, "With this data, we look forward to progressing our regulatory application in China and continue to believe, when approved, a once-daily nebulized revefenacin product will be an important therapeutic option."

Remi relief. Novartis has announced positive data from the phase III REMIX-1 and REMIX-2 studies investigating remibrutinib in patients with chronic spontaneous urticaria (CSU) whose symptoms are inadequately controlled by antihistamines. Remibrutinib met all primary and secondary endpoints at week 121, with around one third of patients achieving complete absence of itch and hives. Angelika Jahreis, Global Head, Development, Immunology at Novartis, said, "We are [...] excited about the prospect to provide a potential new option for patients with CSU who suffer from relentless itch and a life filled with limitations."

IN OTHER NEWS

Antibiotics, HRT, and ADHD drugs among those in short supply in UK this winter because of red tape caused by Brexit

Haleon and Bayer join Blister Pack Collective, a single-use plastic reduction initiative, launched in December 2022 by PA Consulting and Pulpac

Experimental insomnia treatment helps prevent oxycodone relapse in rats, according to Scripps Research study published in Neuropharmacology

Takeda announces late-breaking data from phase IIb study of investigational TYK2 inhibitor TAK-279 for psoriatic arthritis treatment

FDA approves Ogsiveo (nirogacestat) tablets developed by SpringWorks Therapeutics for progressing desmoid tumors that require systemic treatment

Active Manufacturing Responsibility and the Other AMR

Experts from the Access to Medicine Foundation discuss how to reduce the risk of antimicrobial resistance in antibiotic manufacturing

By Marijn Verhoef, Director of Operations and Research, and Martijn van Gerven, Research Coordinator for the AMR Programme, both at the Access to Medicine Foundation, the Netherlands

Antibiotics are a cornerstone of modern medicine, but the rampant rise of drug resistance is threatening their effectiveness – costing lives and endangering millions more.

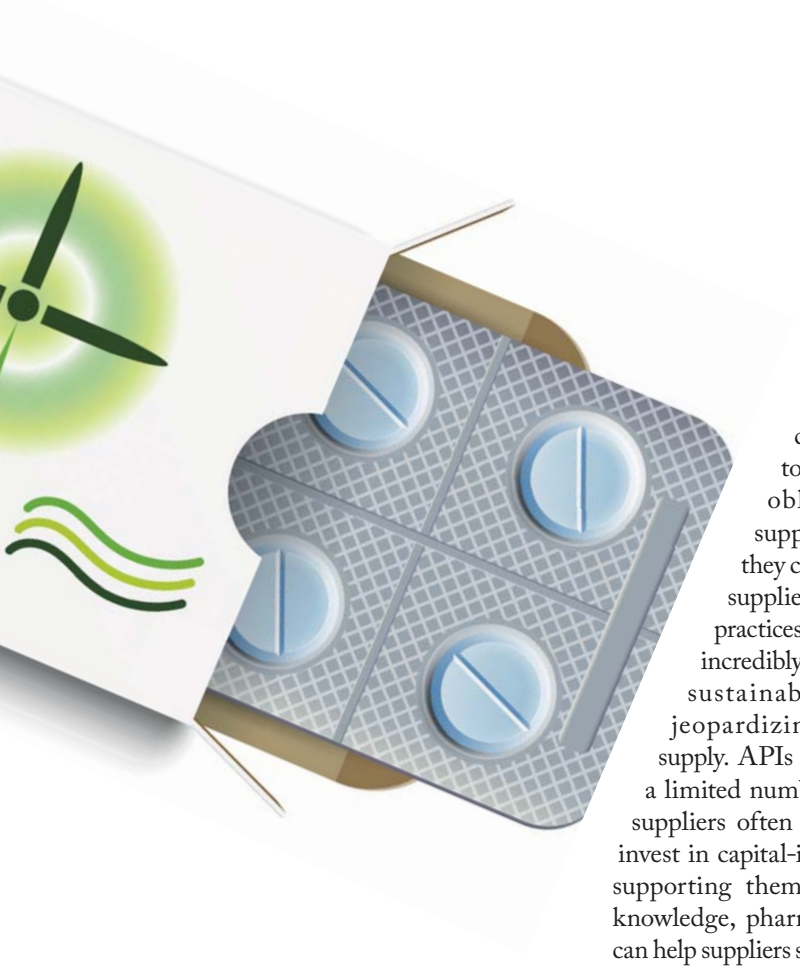
When the Access to Medicine Foundation first started working on antimicrobial resistance (AMR) in 2016, it was estimated 10 million people would succumb to drug-resistant infections each year by 2050. Alarmingly, we are now seeing that lives lost due to AMR may surpass this sooner than we thought. In 2019 alone, 1.27 million people died of drug-resistant infections, disproportionately affecting people living in low- and middle-income countries (1). To minimize the spread of AMR, and to save lives, the development of effective new antibiotics is urgently needed, as is wider access to the full range of antibiotics. This is especially critical in LMICs, where antibiotic access issues are most chronic, and AMR is already hitting hard. But there is another consideration that cannot be ignored; when these lifesaving medicines are produced, antibiotic waste is typically released into rivers and waterways used for drinking water or agriculture. If this waste contains high levels of APIs, it poses a huge risk to the emergence and spread of drug-resistant bacteria, not to mention the harmful impact on the natural environment.

So, what can companies do in the face of needing to expand access to antibiotics, while ensuring their very production doesn't cause unintended harm? The answer is that, ultimately, by managing antibiotic manufacturing waste responsibly, pharmaceutical companies and their suppliers – in India, China and elsewhere – can proactively cancel out unnecessary, preventable AMR risk.

Seizing opportunities

There are several drivers of AMR, and we at the Foundation have long recognized that targeted actions from pharmaceutical companies are vital to expanding access and curbing drug resistance. For nearly a decade, we have been actively engaging large research-based pharmaceutical companies and generic medicine manufacturers on various critical areas, assessing their current activities and highlighting opportunities for further action. We have seen progress, but if we are to stand a chance against the sheer scale and complexity of AMR, companies need to seize every opportunity to tackle it – and when it comes to manufacturing, there are certainly opportunities to do more. A recent report (2) from our AMR Program zeroes in on this issue and examines what antibiotic manufacturers, both large and small, are doing to limit AMR risk in their production processes.

As a vital, logical starting point, companies need to make sure that the



wastewater at their own manufacturing sites is sufficiently treated before they release it. Here, antibiotic discharge limits are the key focus – in other words, making sure excessive levels of APIs that trigger do not enter the environment. Our research has shown that most companies comply with discharge limits in receiving waters – which means they are essentially only assessing once their wastewater is already in a river; for example, where antibiotic concentrations may be subject to dilution. Ideally, companies need to comply with discharge limits directly in their wastewater at a manufacturing site to reduce the risk of AMR more effectively. While we have seen examples from companies that do this, we would like to see more companies comply with limits before their wastewater is released into the environment.

Over and above producing antibiotics at their own manufacturing sites, pharmaceutical companies also contract a wide range of third-party suppliers to produce antibiotics – who they can hold to manufacturing standards to ensure AMR risk is reduced throughout the antibiotic supply chain. Here, companies can choose to enforce contractual obligations to ensure supplier compliance – or they can actively engage with suppliers on how to improve practices. This latter approach is incredibly important in ensuring sustainable change without jeopardizing global antibiotic supply. APIs are often produced by a limited number of suppliers – and suppliers often lack the resources to invest in capital-intensive solutions. By supporting them with resources and knowledge, pharmaceutical companies can help suppliers strengthen their efforts.

Transforming actions into impact

As set out in our report, there are methods and techniques companies can employ to bolster efforts at their own manufacturing sites and those of their suppliers – and the standout examples from companies analyzed in the report show encouraging progress. But beyond taking steps to manufacture responsibly, companies also need to be transparent about their efforts so that successes can be shared – and areas for improvement can be clearly identified by independent organizations. How are they determining discharge levels? What waste management techniques are they applying? Are their suppliers compliant? Without this kind of information, it is very difficult to determine what impact is being made. Unfortunately, companies are still falling overwhelmingly short on publicly disclosing details about their manufacturing practices.

Beyond taking responsibility through voluntary action, demonstrating a commitment to manufacture responsibly is becoming a business priority. There is increasing pressure from procurement bodies on AMR, with manufacturing becoming a keener focus – and regulatory developments are looming.

As identified in our report, procurers are already awarding antibiotic tenders to companies that clearly demonstrate responsible manufacturing practices, and investors are also starting to pay attention to this issue as part of their environmental, governance and social considerations in their investment processes. Companies that do not step up now, will lose out in the future.

The path forward

Antibiotic manufacturers, by-and-large, have embraced the fact that they play a vital role in solving AMR. Our research has shown what companies can – and need to – do. While some are more advanced in implementing steps to manufacture responsibly, it shows progress is possible.

More and more people, especially those in LMICs, will need access to essential first- or second-line antibiotics – not only to treat infections with the right antibiotic at the right time, but to avoid an increase in resistance rates that will affect people around the globe. Scaling up access can be done responsibly.

Now it is a matter of ensuring that the right decisions are made, and the right actions are taken to ensure meaningful, sustainable change takes effect across the entire antibiotic supply chain.

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Best Practice

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Keeping Up to Date with X-Rays

We speak with the BPSA to find out why X-ray sterilization is being considered as an alternative to gamma irradiation

Gamma irradiation (using cobalt-60) is considered the standard method when it comes to sterilizing single use systems, but the high demand has caused supply issues. However, X-ray sterilization can be used as an alternative. To help companies understand more, the Bio-Process Systems Alliance (BPSA) released a guide in 2021 titled: X-Ray Sterilization of Single-Use BioProcess Equipment, Part 1: Industry Need, Requirements & Risk Evaluation.

Now, the BPSA has released Part 2, which focuses on Representative Qualification Data. Readers can expect risk assessments, and data comparing X-ray and gamma irradiated components, generated by multiple component manufacturers for different types of single-use components and materials.

We spoke with Christopher Clark (Executive Director at the BPSA), James Hathcock (Director Regulatory and Validation Strategy at Cytiva), and Samuel Dorey (Principal Scientist Materials & Irradiations Product Development at Sartorius) to learn more.

What are the problems with gamma irradiation?

It takes years to produce colbalt-60 radioisotopes needed for gamma irradiation, not to mention the associated high costs. Gamma irradiation also requires replacing 12.3 percent of the globally installed base per year to account for radioactive decay, whilst navigating the challenges of regulatory approval.

Supply chain management and forecasting needed to meet industry demand has been impressive to date. However, rapid spikes in demand – such as those seen during the COVID-19 pandemic – have made it clear the industry needs alternative technologies that can supplement the growing need and strengthen the overall security of supply for irradiation sterilization.

The continued success and rapid growth of single-use technologies in bioprocessing relies on a robust irradiation-sterilization supply chain. Within our own companies, our sourcing partners suggested the only way to secure the irradiation capacity needed over the next 2-3 years was to embrace alternative (and now mature) technologies such as X-ray. An informed industry approach to qualifying alternative modes of irradiation sterilization may strengthen business continuity in the single-use industry, with the end goal of ensuring innovative patient therapies can be rapidly developed and delivered.

This is not to say that gamma irradiation will go away. Instead, it will continue to be a part of the holistic irradiation capacity solution moving forward, which can be strengthened and complemented by X-ray.

What are the most important points covered in the BPSA guide?

To support the risk assessments needed for implementation, multiple BPSA member companies have been working to generate and share supporting data aligned to the science-based protocol outlined in part one. Data not only help verify the understanding that X-ray and gamma are equivalent, but also show how different labs, components, and suppliers can be summarized and interpreted.

BPSA is not a standards organization; we do not set specific acceptance criteria for the testing results. However, we believe that sharing representative data and interpretations from different parties openly – as opposed to under confidentiality agreements – can help accelerate industry understanding and acceptance. The data include ISO 11137 standard requirements around the irradiation process, such as radioactivity (aka 'activation') and temperature effects, and the industry aligned test methodology to assess the suitability for use of single-use components.

What was covered in Part 1?

A holistic approach to the assessment and qualification of X-ray sterilization entails a fundamental understanding of the impact of X-ray on single-use materials and components — as well as an overall assessment of the final

packaged assembly.

In addition to establishing a cross-industry view on the types of testing that will best assess any potential risk, the working team identified specific tests (i.e., physical, functional, biological, and chemical) to be performed on representative components.

It is expected this risk and data-based assessment of materials and components used in the biotech single-use industry will support the strongly-touted arguments that X-ray is equivalent, or better, than gamma, thereby enabling much of the qualification data already in place for gamma to be leveraged as fully applicable to X-ray. For example, instead of performing animal-based USP <88> testing for biological compatibility, largely considered a requirement from which the industry is looking to move away, the BPSA team recommended non-animal-based cell culture testing associated with USP <87>.

Similarly for extractables and leachables evaluation, an extremely costly exercise that has been a major alignment challenge for the industry over the past decade, the team agreed to recommend a rigorous, but rationalized risk based approach using USP <665> moderate level testing, to verify the impact of the irradiation technologies are equivalent.

Do you expect X-ray technology to be used increasingly in the future?

The simple answer? Yes.

Investments from different service providers in all major geographies show this as a major trend to complement existing sterilization technologies – this includes new X-ray sites in Europe, the Americas, and Asia. Furthermore, with the recent challenges in ethylene oxide emissions, public perceptions, and pending new restrictions, there is a concern that this market, equal in size to gamma irradiation, could add pressure on other forms of contract sterilization. Overall there continues to be strong and increasing global demand for sterilization spanning from food irradiation, medical devices and consumables, single-use, and so forth.

What were the biggest challenges in developing the guide?

The challenges, especially around timelines and sense of urgency were daunting!

Testing single-use components can be very costly, and, in some cases, can require up to a year or more. Suppliers felt they could more readily justify the business case to generate data for their newest products on the market, which – in reality – represented fairly low irradiation volumes than products already on the market. In addition, the testing needed to include a direct comparison of X-ray and gamma-irradiated materials could nearly double the cost of already expensive testing measures. And since the relationships between X-ray and gamma-irradiating test materials at a specific dose were not yet established, this was especially challenging.

Many biomanufacturers wanted to see noteworthy data as soon as possible, whereas the rate at which testing was completed and available was incremental. We also found that having only one or two datasets to scrutinize can easily lead to overinterpretation of small statistically meaningless variations in the data.

I feel that we have addressed both of these with the most recent BPSA paper.

Additional concerns from biomanufacturers include regulatory acceptance requirements – with the subject of prior approval becoming increasingly concerning as the timeline progressed. In our case, we were very fortunate to be closely connected with BARDA. By working together with a small group of end users, suppliers, and industry subject matter experts, we were able to socialize the outputs of the first BPSA paper, representative supporting data, and end user risk assessment concepts with regulators, including the FDA Emerging Technologies Team, EMA Quality Innovation Group, and Japan PMDA. The feedback was largely supportive and has been shared with BPSA (1).

What else are you focusing on at BPSA?

Our focus is currently on how to best track and share X-ray qualification datasets from a large number of suppliers – and for an even larger number of single-use components. There is strong interest in monitoring successful implementations, as well as receiving additional regulatory feedback.

There will also be papers coming out from BioPhorum, which share an elegant risk evaluation strategy based on the types of data expected from the first BPSA X-ray white paper, and how the components are used in actual biopharmaceutical manufacturing processes. This should be a complementary paper illustrating how the outputs of BPSA dovetail and feed well into the other.

Certainly there are many other high-impact BPSA initiatives too, including responses to the REACH proposal to ban all PFAS materials – many of which are critical to the vast majority of medicines on the market (2). Other key initiatives include key guidance papers on integrity assurance for single-use systems, updates to the BPSA Quality Test Matrix, and efforts to ensure and improve sustainability in the biopharma sector.

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NextGen

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In Search of Lost Memory

An insight into the complexities of Alzheimer's disease and the ongoing pursuit for breakthrough therapies

Alzheimer's disease is a puzzle that has confounded researchers for decades. Despite well-documented attempts from high-profile companies to comprehend the nature of the disease, all promising developments have consistently led to disappointing outcomes. And though current therapeutic options can alleviate certain symptoms, they fall short of halting the progression of Alzheimer's altogether. We spoke with Peter St George-Hyslop, a professor of neurology at the University of Cambridge and one of the most cited authors in the field of Alzheimer's research, to learn more about the complexities of the disease.

How did you become interested in Alzheimer's research?

In my third year of study as a medical student, I was asked to interview a lady who had Alzheimer's disease. I was unaware of the condition at the time, but remember feeling completely mystified by her responses. How could a person capable of normal physical movement and answering simple questions have no idea why she was in hospital? Most of her responses were very vague too. I remember reporting to a neurologist afterwards, but frankly, I didn't have a clue what was going on. For the most part, she seemed fine.

The neurologist said, "Did you ask what the date was?" I hadn't, so I asked the question and she did not know. Then the neurologist asked whether I had checked to see if she knew who the Prime Minister of Canada was. Again, I had not asked, and when I did, she thought she knew the answer but was wrong.

The neurologist then said, "This is called Alzheimer's disease. I think it's going to be very common in the future. You had better go and learn about it."

It was a very provocative moment for me. I remember running to the library to find out more, but to my surprise there was only a short paragraph by Alois Alzehimer, which outlined the basic characteristic features of the disease – that was it. I asked myself, how could this strange illness attack and steal the patient of elements we regard as intrinsically human? Their ability to remember, to think and to reason were essentially lost, and yet they maintained the ability to walk around, feed themselves, and do many other such things. It was completely unfair.

Over the years, I received more training; first in internal medicine, then in neurology. I soon realized that Alzheimer's disease was not as rare as had previously been suggested. In fact, it was actually quite common. My curiosity led me to a charismatic neurologist from the Department of Medicine and Neurology in Toronto called Donald Crapper McLachlan. He was also investigating the illness, and it was here that I realized there were some genetic cases that nobody seemed to be following up.

Most of the field at the time was interested in the composition of proteins that accumulated in the brain called amyloid and tau, which contribute to amyloid plaques and neurofibro tangles. These were elements that Alois Alzheimer had detailed when he described the illness in the early 1900s. I thought this was a clever pursuit, but it didn't really answer the overarching mystery of why it happens. I reasoned that if we found that the cause was a defective gene, then we could work forward to understand how that gene causes the illness and leads to the accumulation of amyloid, and so on.

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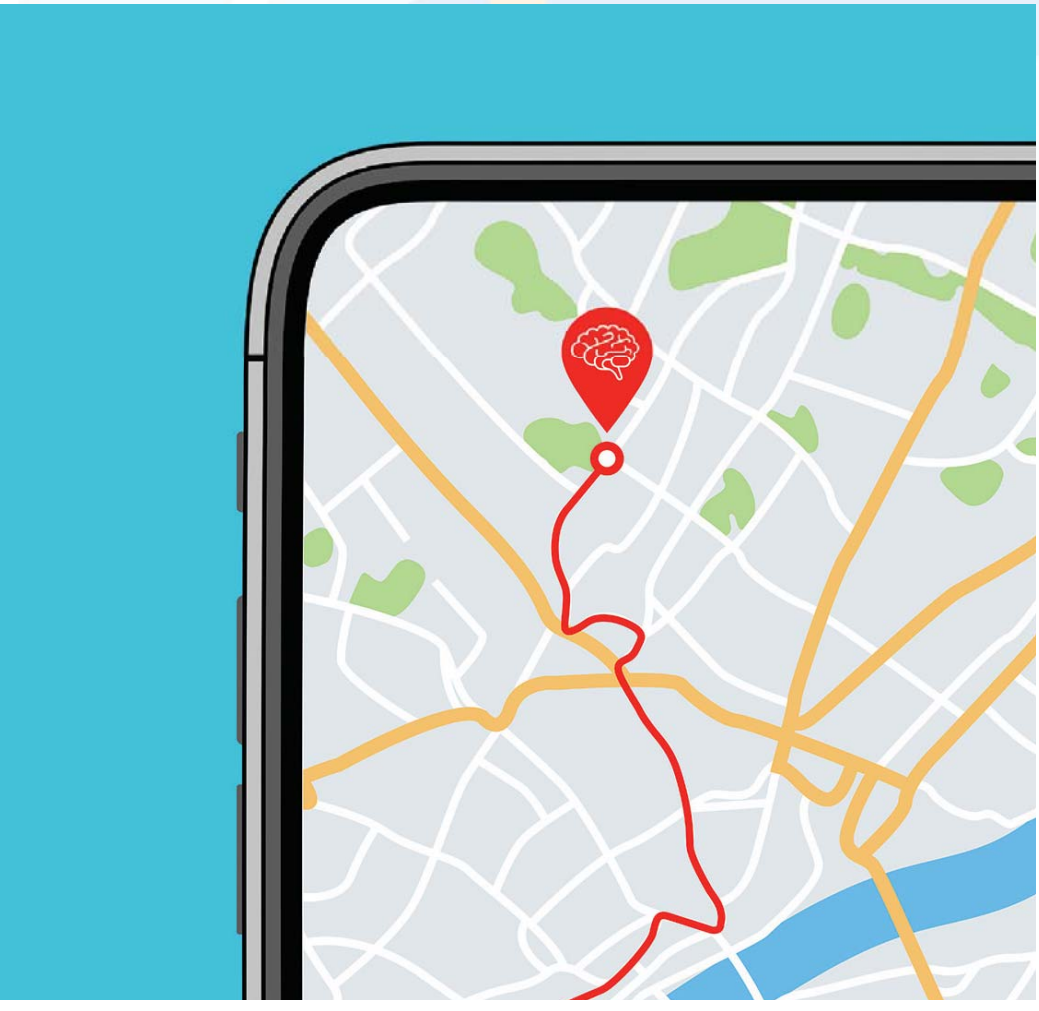

Genetics Network

The Dominantly Inherited Alzheimer's Network (DIAN) study's efforts, led by Washington University School of Medicine in St. Louis, consist of a long-term observational study that aims to identify the biological changes that occur in the development of Alzheimer's disease to improve early diagnosis and to track progression of the disease. The work is conducted in multiple countries around the world and involves researchers, clinicians, genetic counselors, individuals and families, all of whom can connect with each other via the DIAN Expanded Registry and/or through participating research sites for clinical trials or an observational study.

The trial will compare the changes that occur in participants with and without mild Alzheimer's symptoms, who may or may not have an Alzheimer's genetic mutation. All results will be stored in the DIAN Central Archive, an international database that allows qualified researchers to access and analyze the information.

Working out the genetic roots of the illness became my priority. It turned out there was a group at Harvard looking for genetic markers using recombinant DNA technology. Though their research focused on Huntington's disease, I asked whether I could use the same idea to root out the cause of Alzheimer's. Eventually, this pursuit revealed that chromosome 21 was the amyloid precursor protein gene. However, we soon realized that it only described a small proportion of families with familial forms of Alzheimer's, meaning there must be other genes.

Using increasingly sophisticated methods to map and clone the genes of various different loci, we identified the apolipoprotein E in collaboration with Allen Roses, and after that, we discovered the presenilin-1 and presenilin-2 genes. These specific genes are enzymes that cut the protein made by the amyloid precursor protein gene on chromosome 21 to produce amyloid β-peptide (Aβ). Suddenly, we had a real understanding that if a person has a mutation in either of those two genes, plaques would develop and lead to Alzheimer's disease.

We were one of the first groups to show that immunizing transgenic mice, which carried a human APP gene and an illness similar to human Alzheimer's disease, would essentially remove or prevent the formation of the amyloid pathology and improve their cognition. This was the starting point. Now, we're interested in about 12 different genes focused on the role of microglia, which are cells in the brain that remove infectious agents and toxic proteins. Research suggests that mutations in these genes negatively impact the microglia and prevent the clearance and protective function. Personally, I believe manipulating the immune and neuroinflammatory aspects of this

disease will be the second therapeutic avenue of approach.

You've said that fighting this disease "is more complex than battling cancer." Why is Alzheimer's such a difficult area of drug development?

The therapeutic options against cancer are multitudinous. You can attack cancer in various ways, biopsy a physical target, and understand its cellular makeup. With Alzheimers – up until very recently – even the first step of understanding the disease was difficult because the diagnostic tools were quite vague.

Understanding when someone has dementia is clear, but as there are many different causes it's difficult to be sure a patient has Alzheimer's disease. This is becoming better understood with improved biomarkers, but one of the reasons early vaccine trials failed is probably because people were recruited using poor diagnostic criteria. Getting clean cohorts where you know what participants have, and you know what you are treating, remains a challenge in many clinical trials.

Furthermore, Alzheimer's disease has many different causes, including both genetic and environmental. Researchers must account for the problem of inhomogeneity in cohorts, and the likelihood is that some treatments may work for certain types of Alzheimer's disease but not others. On top of this, there are also numerous stages of the disease, with various components that can go wrong. For example, you could target the amyloid, but if tau or inflammation is already present without treatment, it may self perpetuate. Simply put, even if you have successfully engaged in the target you intended, you may not have stopped other aspects of the disease.

Finally, Alzheimer's is a chronic disease and there is probably a 10 or 15-year preclinical period where the disease progresses without patient awareness from a functional point. By the time the patient requires treatment, they usually have a lot of existing damage, and providing an optimal treatment at that stage is unideal.

Ultimately, the diagnostic difficulties and the multiplicity of the disease process makes it a much more intractable target than cancer. At present, you must follow a large patient population for six to 12 months to see cognitive changes, and these factors together result in highly expensive clinical trials. This is a huge barrier to developing treatments without notable risk.

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Where do you think the priorities need to lie – in both academia and industry – if we are to see a real change in treatments for neurodegenerative diseases?

There's a shared understanding in both academia and industry that treating the disease is dependent on early detection. In fact, there is currently a huge emphasis on developing appropriate biomarkers to do this.

First and foremost, I'm a great fan of the pharmaceutical industry – they achieve things no academic or small biotech company could ever do. However, understanding the very basic aspects of Alzheimer's disease is where you're going to generate new insights and targets. We all understand that microglia are misbehaving; we all understand that tau is accumulating; we understand that A beta Tdp43 alphaCNuclean are accumulating. What we don't understand is how they all link together. Understanding what links one to the other, and how to break up those interactions, is going to be very expensive, but ultimately profitable, for the pharmaceutical company – as well as the basic science. In essence, funding is at the crux of everything, and Alzheimer's is no different.

More positively, ongoing trials from the DIAN (Dominantly Inherited Alzheimer Network) study are approaching people with mutations in single genes (i.e., presenilin, AVP, or TREM2). Their research targets preclinical carriers for treatment and I am excited to learn whether treating just the APP aspects of the disease will be successful.

What are the most promising therapeutic avenues for interventions or preventive strategies?

There are new cellular models being developed around organoids, assembloids, IPSCs, and mixed models, which require the basic fundamentals of science to be married with application-based science. I think this could be transformative. Indeed, even if we are successful in treating patients in the disease process, there will be people

that have a certain amount of injury to the brain. Therefore, parallel work done on repair, whether through the implantation of new cells, or by retraining networks is equally important. Another noteworthy suggestion includes developments coming to the fore from basic neurobiology that focus on transcriptomics or omics.

What is your view on emerging treatments that target amyloid beta?

The development and progression of A beta antibody treatments show two things: 1) It may be possible to accelerate the removal, or prevent the accumulation of neurotoxic proteins; and 2) A beta is, in fact, a central player in the disease.

In my opinion, these developments validate the immune approach. It suggests that A beta is a reasonable target and can motivate other strategies for treating the amyloid aspect. However, antibodies alone are insufficient; they can only slow disease progression. Combination treatment, therefore, seems to be the most viable avenue to target different parts of the disease.

Lecanemab has perhaps established a minimum threshold. If you can do better, you'll probably get registered. Whether it will be a viable therapeutic or prophylactic remains to be seen – and it is quite expensive. However, it is definitely a significant milestone.

What qualities do you think are essential for a researcher or a scientist?

Generally speaking, there are three qualities I believe to be particularly important.

- Curiosity. This is necessary to motivate you beyond the grain of current understanding, to resist status quo, to persevere, and ultimately fuel your desire to learn more about a selected research topic.
- Resilience. There's a joke that research contains the prefix "re" because you keep re-doing things until you find the right answer, and I think that's true. You need to be resilient because many of your questions, approaches, or attempts will fail. But with failure, there is eventually success. It is important to be able to bounce back, and to find new solutions to complex problems.
- Creativity. Researchers with the capacity to think outside the box, set aside dogma, and resist following the field in pursuit of innovatory explanations are at the core of what it means to be a scientist.

Taking Sustainability to Heart

Sitting Down With…
Hanns-Christian Mahler,
CEO of ten23 health

Why do you feel so strongly about sustainability?

Many people – including myself – have climate anxiety. Here in Switzerland, I have noted climate changes and I often wonder what this will mean for my children.

Here's a fact I have never forgotten: in 2015, the pharma sector created more than 50 megatons of carbon dioxide emissions, which, per revenue, is more than the automotive sector. Many people in pharma hide behind the fact that the industry does such important work for human health. Yes – we must prioritize and ensure patients and safety, but we also need to ask what we can do to lessen the impact of the industry on the environment.

Given the unusually high focus on sustainability, did the ten23 health concept present any challenges when you set the company up?

When you talk with investors, the first discussion is typically financial in nature. We aren't a non-profit organization, so finances are definitely important! But I also believe in giving back. We want to create fun jobs for our employees. We want to give back to the region by creating jobs here. And we want to give back to the planet. Fortunately, our investors – 3i – highly appreciate this, and have also done their own training and webinars on the topic of sustainability.

The first thing I did was sign a contract for plastic offsetting. We had no operations. No people – but I purchased around 10 tonnes of plastic trash! The investors have been very happy with our approach. (And I'm very happy they didn't fire me!)

At ten23 health, we see an opportunity to go further than what existing legislation demands. We place a huge emphasis on being sustainable. My motivation is to leave a heart print for our employees, competitors, and customers, on how to do things.

What specific actions have you taken to reduce your business's impact on the environment?

Sustainability goes into every corner of our organizational design and sites; we have a big focus on monitoring, measuring, and innovating around issues.

We measure and report on a facility basis for energy and water consumption, and use ratios to measure total consumption and total energy. For example, when we look at our production facility, we look at total energy usage divided by the number of output, such as batches that we've produced. We also look at total site usage divided by generated revenues and by the number of employees. As the years go on, the ratios should go down as energy utilization improves.

We also care deeply about sources. We use 100 percent natural energy sources, and we also consider things like choice of printing paper, toilet paper, and coffee. Many companies use Nespresso machines and people tell themselves the capsules are recyclable, but we have a Fairtrade coffee with local roasting – and the grounds go to on-site composting.

What challenges do companies face in being more sustainable?

It can be hard to change what you already have. The blessing that we have at ten23 compared with other companies is that we didn't need a huge transformational undertaking with painful step-by-step planning and prioritization. We started from scratch with sustainability being at the heart of ten23 from the very beginning.

We took over the rent of a site that was previously run by a different company in Basel. The labs were beautiful – but the hallways, restrooms, and meeting rooms were clearly never designed to be shared with the outside world. There were many opportunities during the refurbishment to replace old lamps with motion-controlled LEDs and other actions that helped to significantly reduce our energy consumption.

Where do we put the printer? Do we even buy a printer? What paper do we use for the printer? Which coffee machine do we buy? It's not as if we had 15 Nespresso machines that we needed to figure out what to do with when moving to an alternative.

What simple steps can companies take to reduce their environmental footprint?

First of all, it only works if the management and the board are in alignment. Switzerland actually offers board training in the area with "SBA2030;" for all companies that want to go into sustainability, I recommend that you get your board trained.

Many companies have plans that stretch up to 2030, 2040, or even 2050. Certain things, such as product life cycle assessments, will take a long time, but there are quick fixes you can make in other areas. Go into your own operations and look at the simple changes you can make. Check your energy consumption; check your light sources; turn off the heaters; consider closing your site at Christmas when only a small number of people are working. Call your energy supplier and ask questions about their sources. Get yourself switched to renewable energy sources. You'll need management on board because the price may be higher short-term, but the industry cannot keep optimizing their margins for the sake of leaving trash behind for the next generation.

How have people reacted to ten23's work?

I get approached by people who want jobs because they are excited about what we do. We've had a lot of feedback about what we do and I think it confirms we're taking the right approach. People seem really inspired.

There have also been some negative comments. People tell me that plastic will never go away in big pharma so we shouldn't make a big deal about it. Others tell me that everyone is interested in sustainability and ten23 isn't so special (my response to that: "How many CDMOs do you know that are doing their own composting?"). I don't take any of these comments and questions personally – and it's great to see that so many companies today are thinking about sustainability and filing sustainability reports. But we need to be wary of greenwashing. Actions need to follow words.

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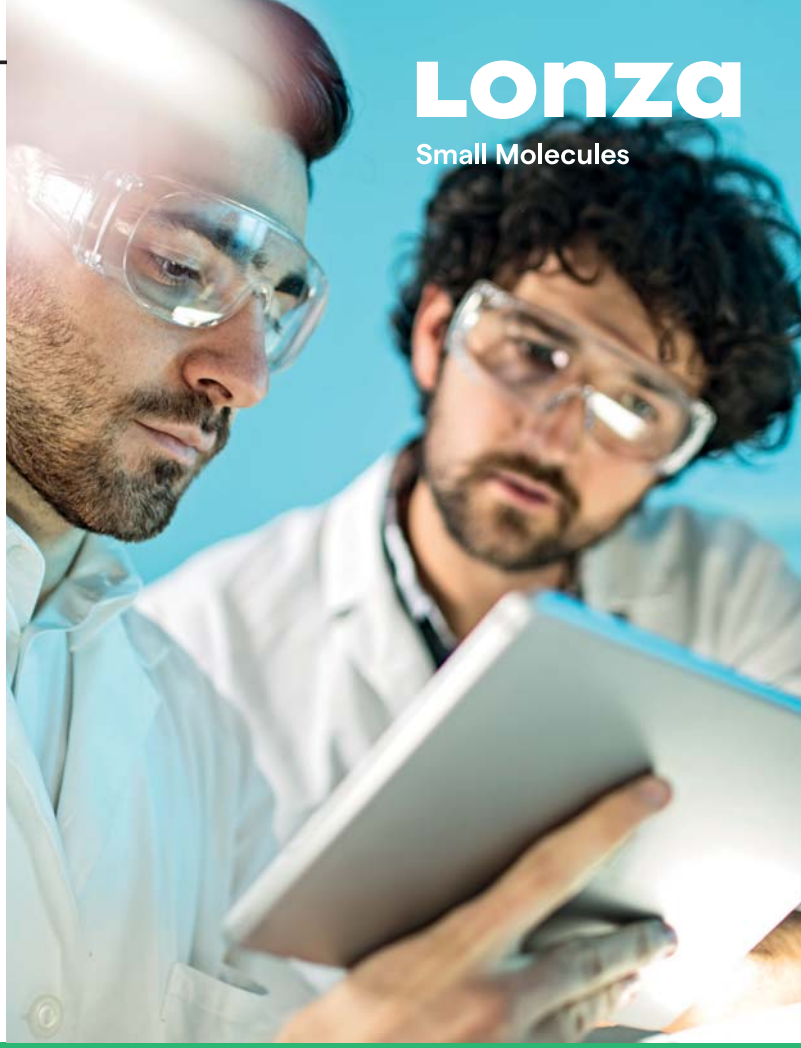

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