MARCH / APRIL 2024 # 96

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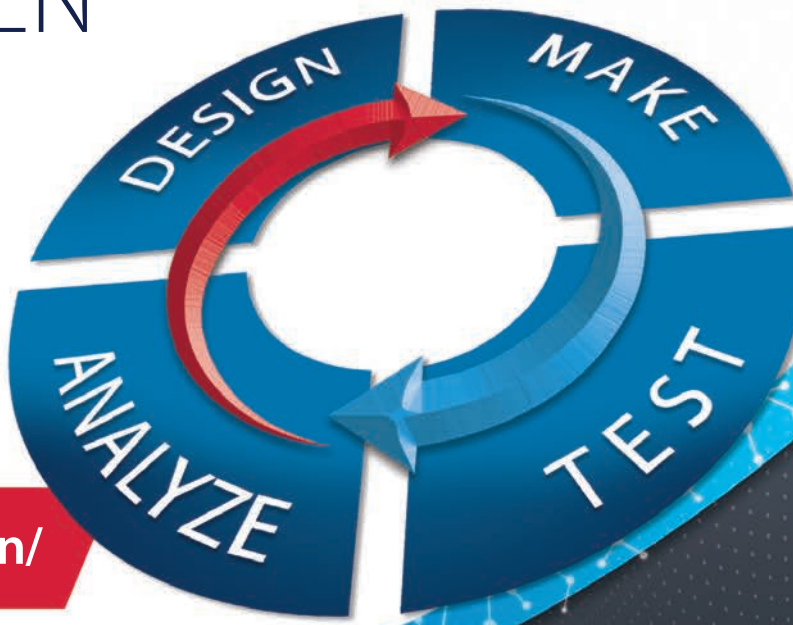

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Potentially Unprecedented

US conservatism takes on the FDA, progressives, and mifepristone in the Supreme Court

At the end of March, the US Supreme Court heard oral arguments in the case involving abortion pill mifepristone. No final decision had been made at the time of print (final decision anticipated in June), but justices seemed to be swaying towards declaring that plaintiffs had no legal basis to sue in a federal court.

The lawsuit was initiated by the Alliance for Hippocratic Medicine (AHM), which was formed in 2022 and seems to mainly consist of anti-abortion groups. AHM believes that mifepristone prescription goes against the Essential Hippocratic Oath and is therefore unethical. With the AHM translation of the oath stating, "I will not help a woman obtain an abortion" (other versions state: "I will not give to a woman a pessary to cause abortion"), its case questions both the drug's safety and the FDA's expanded access to it.

Mifepristone was approved almost 25 years ago and is therefore outside of the FDA statute of limitations of claims, which is six years. A Trump-appointed federal judge, Matthew Kacsmaryk, based his previous ruling in Texas on discredited studies and "data" obtained from sympathetic, anonymous online content, and it has been suggested that Kacsmaryk didn't have jurisdiction to hear the case at all.

For the pharma industry, this hasn't just been about the ethics of abortion. If FDA approval of mifepristone is overturned, it could set a precedent for other drugs. In 2023, BIO's Rachel King said, "For a court to invalidate the approval of a drug that was reviewed and approved more than two decades ago is without precedent. As legal scholars have noted, the courts do not have the medical expertise to make these types of scientific determinations (1)."

The defendants in the case, the FDA and Danco Laboratories (mifepristone's manufacturer), could see the case thrown out – or at least found in their favor. US Solicitor General Elizabeth Prelogar told Supreme Court justices that any other outcome could "severely disrupt the federal system for developing and approving drugs" and "inflict grave harm on women across the nation."

However, there could be more arguments to come. Specifically, the Anthony Comstock Act (2), which was passed into federal law in 1873 and essentially prohibits the sending and receiving of materials designed or intended for "the prevention of conception or procuring of abortion," is expected to form the basis of the AHM's next argument.

Rob Coker
Deputy Editor

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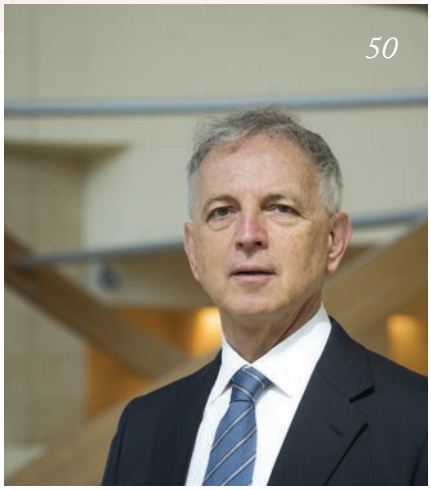
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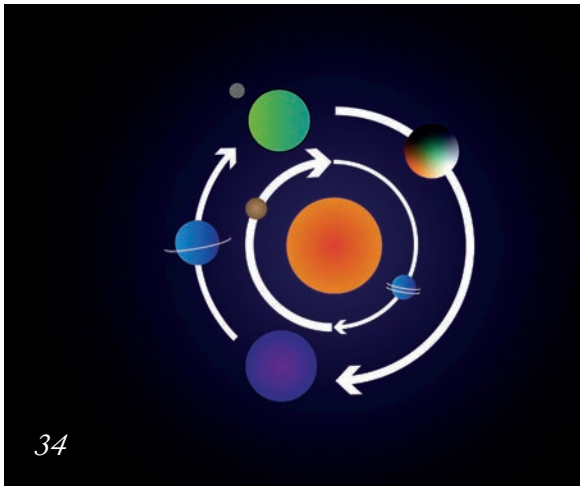
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NextGen

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the Medicine Maker

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Change of address julie.wheeler@texerepublishing.com
The Medicine Maker, Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries
www.texerepublishing.com | info@themedicinemaker.com
+44 (0) 1565 745 200 | sales@themedicinemaker.com

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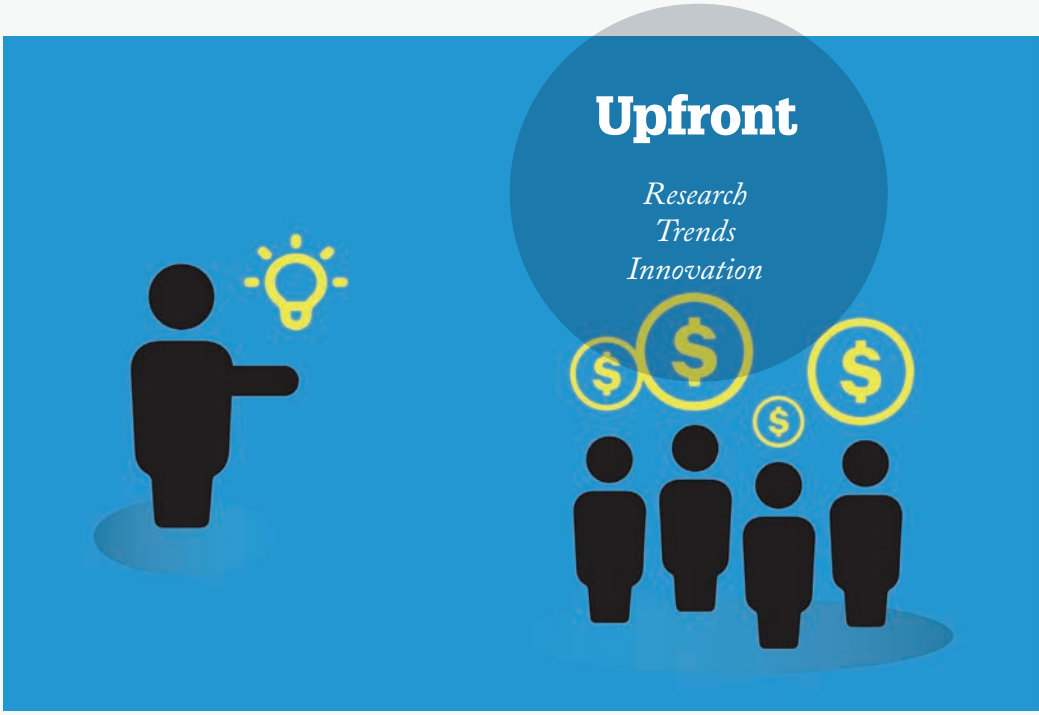


Open Innovation Against Epilepsy

Angelini Pharma launches crowdsourcing project to tackle drug-resistant epilepsy

Italy-based Angelini Pharma has challenged the crowdsourcing community website Wazoku to pool its collective talent and identify pharmaceutical-based solutions for drug-resistant epilepsy symptoms, including seizures. Wazoku was launched in 2011 with a big mission: to prove that human ingenuity and collaboration can overcome any scientific challenge. It has already been used by various pharma companies, including GSK and AstraZeneca, and even NASA.

Angelini's Chief Scientific Officer Rafal Kaminski said: "Through this open innovation challenge, we expect to identify innovative digital solutions with the potential to improve the identification of new targets in drug-resistant epilepsy that can be validated preclinically. This would help us build our early-stage pipeline, thus supporting our efforts in brain health."

Innovation Consultant at Wazoku Dino Ribic agreed: "Whether it's helping to manage an aging population, tackling mental health, addressing inequity in access to healthcare and medicine or combatting the rise of infectious diseases, open innovation is increasingly invaluable to the pharmaceutical sector and the wider world. Progressive companies like Angelini Pharma have recognized the benefits of collective intelligence, and I can't wait to see what the Wazoku Crowd delivers in this instance."

The project has set a number of focuses, including the diversity of genetic architectures, the variety of targets and pathways potentially involved in different subtypes of epilepsy, and the limited amount of human epilepsy transcriptome and multiomics data.

This is a Prize Challenge, so Angelini and Wazoku have requested written proposals. In submitting a proposal, any challenger with a credible solution grants a royalty-free, perpetual, and non-exclusive license to Angelini for the use of the information included. With a total payout of up to $25,000, citizen scientists are likely to be as tempted to the prize money as they are to the challenge of coming up with a practical and innovative solution.

Open innovation has proven successful in generating innovative solutions in the pharmaceutical sector before, whether through accelerating drug discovery and development – as in the case of AstraZeneca's call for ideas in its molecular glue drug discovery project – or by navigating operational challenges, such as costs and recruitment, as highlighted by Janssen Pharmaceuticals.

TIMELINE

Measles in Time

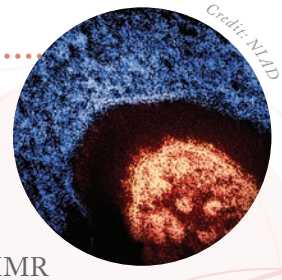
A brief history mapping the fall – and rise – of a previously forgotten, potentially devastating childhood illness

1963

First measles vaccine licensed for public use by John Franklin Enders

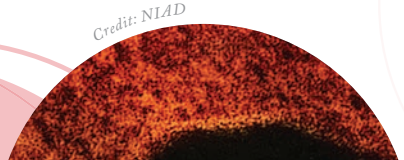
1971

Maurice Hilleman develops combined MMR vaccine


Credit: NIAD

1991

Measles elimination efforts in the Americas Region begin


Credit: NIAD

BUSINESS -IN-BRIEF

A look at some of the biggest business headlines in the industry

- The FDA continues to look into quality and performance issues of plastic syringes made in China, and has issued warning letters to Jiangsu Shenli Medical Production, Medline Industries, and Sol-Millennium Medical. The agency also advises companies to only use plastic syringes from China until they are able to transition to alternatives. The problem does not include glass syringes.
- AstraZeneca plans to acquire radioconjugate specialist Fusion Pharmaceuticals. The company believes that radioconjugates have "many potential advantages compared to traditional radiotherapy including minimising damage to healthy cells and enabling access to tumours not reachable through external beam radiation." Fusion's most advanced drug candidate is FPI-2265, for metastatic castration-resistant prostate cancer.
- Genentech/Roche's Vacaville facility in California will be sold to Lonza for $1.2 billion. The site is one of the world's largest biologics manufacturing facilities (by volume). Lonza says it will also invest CHF 500 million (around $557 million) to further upgrade the factory. The Roche products currently made at the site will now be supplied by Lonza but phased out over time.
- The US Court of Appeals for the Second Circuit has reversed the decision of a lower court in an antitrust case involving Novartis and Regeneron. Regeneron had accused Novartis of using patents to delay market entry of Regeneron's Eylea. The lower court had dismissed the case, but the decision from the appeals court now means that Novartis must return to court.

Best Practices From WHO

WHO's compendium on quality assurance updated

The WHO has released the 10th edition of its compendium on the quality assurance of pharmaceuticals – designed to help regulators, pharma companies, healthcare professionals, and procurement agencies to uphold globally acceptable standards of GMP. The updated compendium includes updates and new texts. "It now includes forty-five guidelines covering topics related to GMP and the inspection of pharmaceutical manufacturers and distribution channels. Among these guidelines, ten have been revised to incorporate the latest advancements and address emerging challenges in the pharmaceutical industry, while eight new guidelines have been introduced to address previously unexplored areas," says the document.

New topics include GMP for investigational radiopharmaceuticals and medicinal gases, recommendations on environmental aspects for the prevention of antimicrobial resistance, health-based exposure limits in cleaning validation, and good practices for research and development facilities.

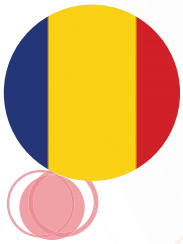
The document can be downloaded at: rb.gy/2zxzu2

1998

Paper published in *The Lancet* fraudulently links MMR vaccine with autism

2016

Americas Region declared free of endemic measles



2023

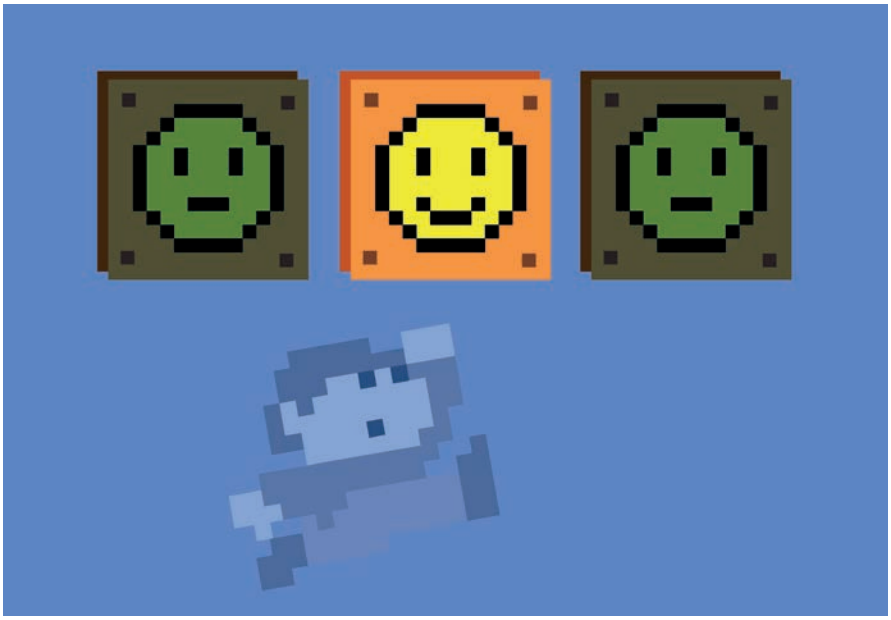
1,755 cases of measles reported to ECDC from Romania in 2023

2024

Measles cases in US for first quarter match year total from 2023

Paging Dr Mario

Understanding the results of a viral study on using video games to treat depression



After researchers from the University of Bonn, Germany, published a study titled "Effects of a video game intervention on symptoms, training motivation, and visuo-spatial memory in depression", consumer media headlines began touting that the video game "Super Mario Odyssey" could beat depression.

"Interpreting media headlines about scientific studies, such as those concerning our research, requires caution," lead researcher Moritz Bergmann explained. "It's important to understand that a video game alone is not a cure for major depressive disorder (MDD)."

However, the results of the small study are compelling. The study explored an adjunct treatment combining usual clinical care with video gaming therapy using "Super Mario Odyssey." This approach showed promise in improving depressive symptoms and visuospatial memory performance in patients.

Participants with MDD were assigned to one of three study groups: i) a video gaming group that played the game alongside normal clinical care, ii) an active control group that used a computerized training program called CogPack that focuses on exercises for attention, memory, visuomotor skills, etc – again alongside normal clinical care, and iii) a "treat–as–usual" group that only received standard clinical treatment (psychotherapy and/or pharmacotherapy).

The 3D gaming group performed very well. In fact, a statistically significant decrease in depressive symptoms was only found in the gaming group (dropping from 100 percent at the start of the study to 57 percent at the end). The gaming group also showed on average higher levels of motivation than the CogPack group. For visuospatial memory functions, all groups showed some improvement, with the CogPack group seeing increases across all variables.

Bergmann added, "Despite these promising results, we must be cautious about generalizing because of limitations; for example, the small sample size and the unblinded nature of the study, which could introduce experimenter and expectation biases. Further research with larger sample sizes, blinded designs, and follow-up measurements is essential to validate the findings. That said, the initial results are encouraging, pointing towards new avenues in therapy."

You can read our interview with Mortiz Bergmann online: tmm.txp.to/super-mario

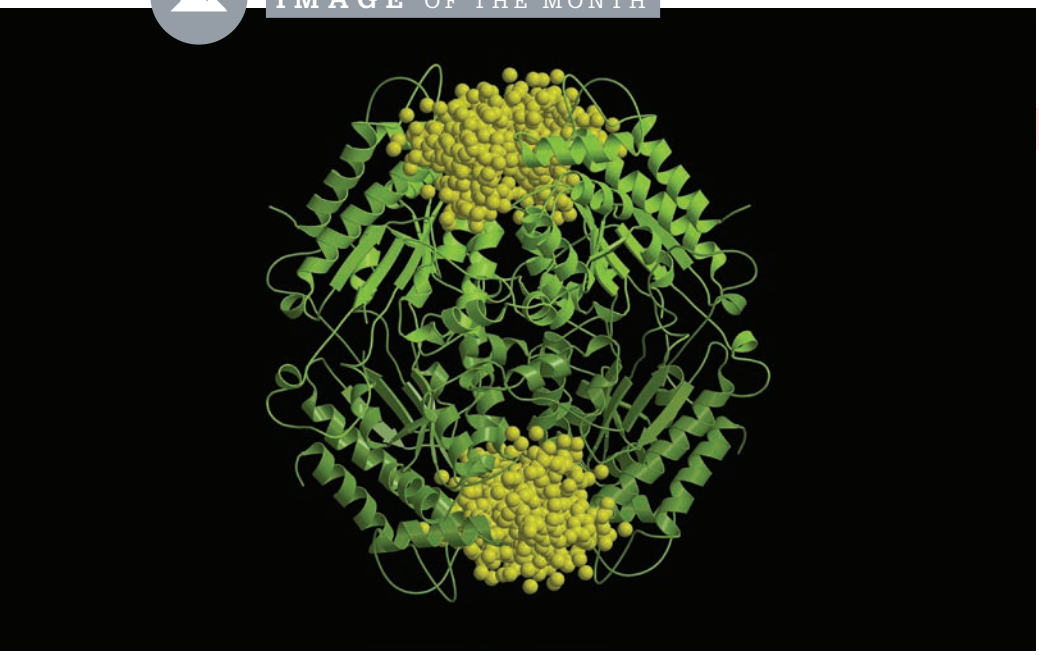
Food For Thought (and Sustainability)

Biological engineering project seeks to use food by-products to create antimicrobials

Researchers in the UK from the University of Strathclyde, University of Surrey, and GSK have received a grant of £1 million to develop a less carbon-intensive process for manufacturing antimicrobial drugs from bacteria. The team will use biological engineering to enable food by-products to be used as a feedstock for the bacteria. According to lead research Paul Hoskisson, a professor at Strathclyde, there is a need for more sustainable industrial feedstocks for fermentation processes that do not compete with food chains. He says, "Our approach will learn from existing industrial strains and use metabolic modelling to inform us on appropriate engineering strategies for the development of new strains of antibiotic producing bacteria."

The team also hopes that the process will be translatable to other types of drugs made in Streptomyces bacteria, such as anti-parasitic, anti-cancer, anti-fungal and immunosuppressant drugs – and that it will be a more cost-effective form of production.

IMAGE OF THE MONTH



Mimosa

Inspired by nature, Giedrė Tamulaitienė uses X-ray structural analysis and cryogenic electron microscopy to generate artistic images of protein structures

Credit: Giedrė Tamulaitienė

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

QUOTE of the month

"I was astonished by the audience and the attention that our work received during this period. This highlights the public's interest in innovative approaches to mental health, but it also underscores the importance of accurately interpreting scientific studies – especially when they make headlines."

Mortiz Bergmann – talking about the experience of having a research study go viral in consumer media. Read more: tmm.txp.to/super-mario

Credit: Tetyana Yana-t Petruk

Mobilizing Against Measles

Outbreaks of measles are increasing across the globe

Such is the severity and proliferation of measles cases in the US, the National Foundation for Infectious Diseases has urged people to remain up to date with MMR vaccinations – a legacy public health recommendation from days when such reminders were deemed obvious rather than necessary.

Although measles was declared eliminated in the US in 2000, there were 41 reported cases in the US in the first two months of 2024, compared with just 58 cases in the whole of 2023 (1). Canada is also seeing an increase in cases, with 17 confirmed this year, as is England, where a total of 368 cases were confirmed in 2023. Other regions also face problems. In Africa, the Institut Pasteur de Dakar, with funding from the Bill & Melinda Gates Foundation and in partnership with Biovac, plans to manufacture measles vaccines in an attempt to keep African vaccine production independent of imports. South Sudan has one of the continent's most severely affected populations, where health director for the city of Dalang Noura Faroug has reported an "acute shortage of medicines, vaccines, and other medical aids" (2).

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In My View

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

The Ethical Issues of Advanced Medicine

Cell and gene therapies open up important questions that must be answered

By Sumukhi Sreevatsan, General Manager at IMAPAC

How do we encourage the development of new cell and gene therapies without compromising our social ideals or the wellbeing of individuals? In my view, there are two significant ethical issues that must be addressed with advanced medicines: i) informed consent and ii) the cost of therapies.

Given that cell and gene therapies rely on manipulated genetic materials, there are fears that the industry lacks the knowledge to predict long-term impacts (1), which creates challenges for informed consent. Informed consent requires patients to be given all possible knowledge of what the treatment involves, including benefits, risks, and alternatives. In a sector that is still developing and changing its knowledge rapidly, such risk assessments are difficult to accurately make, and can quickly become outdated with new patient outcomes and results. For instance, the Francis Crick Institute's attempt to develop a new germline therapy found that 16 percent of altered embryos in the lab saw mutations that would have been undetectable by conventional methods (2).

The European Commission has been pushing to overhaul current regulations to ensure they remain fit for purpose for innovative medicines and to provide clearer standards for industry leaders to assess their peer's ethical adherence (3). Separately, the FDA released a new guideline document – "Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products" – in 2022 as part of their own regulatory upheaval. The document offers a codified guideline, based on discussion from leading experts, on how CAR T focused on cancer treatments can be made safe.

Informed consent in cell and gene therapies is a topic that I expect to remain complex for the immediate future. However, regulatory reform championed through sector

"Risk assessments are difficult to accurately make, and can quickly become outdated with new patient outcomes and results."

collaboration – and supported by leading biopharmaceutical professionals and other companies – will, in time, help address ongoing concerns and inform future developments.

Improving standards of communication and regulation within the biologics industry should also help address another crucial ethical concern with cell and gene therapies; how to ensure fair access.

Analysis from the Institute of Clinical and Economic Review indicates that the average price of a new gene therapy is $1-2 million per dose (4), and there are fears that such expenses will increase current healthcare inequalities. Without funding policies in place, treatments may only be accessible to the wealthiest sections of society.

Cost–benefit analysis is a fundamental component of new medical developments, but this is particularly resonant in regard to therapies at the cutting edge of scientific developments with very high manufacturing costs. The high prices are understandable, given the technical and specialist knowledge that underpins these developing therapies, but what if those who would benefit most from the therapies have the worst access to them? Such a concern first became apparent in 2015 when Glybera, the first gene therapy approved in Europe, was priced at €1 million per dose.

Regulatory bodies and industry associations can encourage more equitable access. In the UK, for example, the Bioindustry Association has advocated for the NHS and other healthcare organizations to implement new payment models to defer the large upfront costs of treatments through payment plans and discounts (5). The success of such an approach, however, will depend on collaboration and communication across the entire value chain – from government departments to healthcare bodies and manufacturers. Together, we must aim to create a system that balances financial motivations with ethical adherence.

An evolving biologics sector needs to ensure that its ethical regulations remain robust, while striving to distribute them fairly – all without limiting future development. Striking this balance between innovation and ethics is complex, but I am certain that greater industry cooperation is the foundation of a satisfactory answer to such questions.

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Can AI Tackle Drug Shortages?

The role of artificial intelligence in getting more medicines to market

By Jo Varshney, CEO at VeriSIM

It's been more than a year since the onset of some of the worst drug shortages in US history. You may think I'm referring to the shortage of Adderall – the most commonly prescribed drug for the treatment of attention deficit hyperactivity disorder (ADHD), which was confirmed by the FDA on October 12, 2022. Though the continuation of that shortage (and the multiple failed recovery efforts) is mortifying at best, I'm actually referring to the thousands of other drugs – including lifesaving and life-improving treatments for cancer and hundreds of diseases – that should be undergoing research trials right now. Strangely, this problem hasn't received anywhere near the same level of attention in the media.

Consider this: in October 2023, there were 16 FDA-approved oncology medications experiencing shortages (up from 11 in July 2023). The situation is a huge problem for patients and the doctors who treat them. In every case of a drug shortage, doctors are forced to choose another means of treatment (a different drug or another type of therapy) or to forgo treatment until options improve. We've seen how well that works with drugs like Adderall (it doesn't). In fact, the Adderall shortage had a cascading effect; when doctors started prescribing other ADHD medications, it resulted in widespread shortages of multiple medications. But when it comes to even more specialized drugs, like cisplatin, the outcome can be even more somber. Cisplatin – a powerful chemotherapy drug frequently used for the treatment of multiple cancers including ovarian, bladder, brain, throat, cervical, and lung cancer

"AI methodologies can speed up the process of developing new applications for already-existing medications by running simulations that perfect dosing across multiple application types."

– fell into short supply in December 2022, when manufacturer Intas Pharmaceuticals ceased production in the face of FDA concerns over quality. The move immediately suspended US access to 50 percent of its cisplatin supply, leaving cancer patients with suboptimal treatment options, and no other manufacturers to step in.

Quality concerns, capacity-building failures, and cascading effects aren't the only reasons that drug shortages happen or worsen. In fact, until recently, regulatory restrictions were the most cited precursor to drug shortages.

The bigger issue, and the reason we fight the same drug shortages year after year, is that we simply rinse and repeat the same solutions that never hold. The only way out of the cycle is to solve the real problem: there aren't enough medications to choose from. And that problem starts long before drugs ever hit the market. In fact, just one out of 10 potential drugs successfully clears preclinical or clinical trials. So far this year, the FDA has only approved 43 novel drugs for the treatment of human medical conditions. We may never know how many drug candidates didn't make it through clinical trials or how many lives they might have saved. Perhaps more sobering is the reality that most drugs fail for completely preventable reasons, including human error, flawed study design, or underpowered clinical trials with too few participants.

There are ways to fix the problem and give every useful drug candidate a chance. Translational medicine concepts are already being applied to drug trials to help reduce human error. And AI is being deployed to make the drug development process more efficient than ever. My own company, VeriSIM Life, is deploying hybrid AI methodologies to identify the most effective compounds and combinations with the fewest side effects. Importantly, we're making it happen before ever involving a human patient – a move that de-risks the experimentation process. When applied correctly, our approach could significantly reduce time-to-market (a process that presently takes 10–12 years on average to complete).

But even a shortened timeline for drug development is a long time to wait when current treatments are already in short supply. And that's why applying AI to reformulation – a capsule to a patch or a caplet to an injection – could come in handy right now. AI methodologies can speed up the process of developing new applications for already-existing medications by running simulations that perfect dosing across multiple application types.

Although the focus right now is on moments of hope, such as the recent approval of multiple generics for Vyvanse (an alternative to Adderall), shortages for hundreds of other medications will not only continue this year but also circle back around unless we do something about it. In my view, that means thinking outside of the box to change the drug industry from the bottom up.

AI can really help. So the big question is whether the industry will move quickly enough to change a paradigm in desperate need of a technology-led evolution.

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POWER *List*

Thirty amazing individuals. Thirty very different journeys on the way here. One big commonality: they all thoroughly deserve a place on The Medicine Maker Power List.

BY ROB COKER

It's not all about patents and products. It's people who drive innovation and inspiration in the pharma industry, helping bring groundbreaking new medicines to patients in need.

Once again, we invited The Medicine Maker audience to throw the spotlight on their inspiring colleagues, peers, leaders, and mentors by submitting nominations for our annual Power List – and they did not disappoint. Here, we applaud 30 incredible players making waves in small molecule, biopharmaceutical, and advanced medicine drug development. In an age of political polarity, ongoing and emerging challenges to human health, conflict, and huge shifts in the ways we work, our Power Listers continue to roll with the world's punches, using their hard-won capital to generate positivity, inspiration, and innovation. Welcome to the 2024 Power List!

This list is also available online at https://themedicinemaker.com/awards/power-list/2024

SMALL *Molecules*

Marc Brown

Co-Founder, MedPharm

Marc Brown co-founded MedPharm in August 1999, was CSO until 2020, Board Director until 2024, and he remains Chair of MedPharm's Scientific Advisory Committee. Brown was instrumental in establishing MedPharm's principles and ethos, and has been a guiding force behind many of its scientific developments, innovations, and intellectual property. To date, he has been involved in the pharmaceutical development of over 60 locally applied medicinal products that are on the market in Europe, America, and Japan. He also acts as CSO to Mosanna Therapeutics AG, supporting the development of their sleep apnoea medicine.

"As knowledge in molecular biology and genetics grows, the biopharma potential market increases, but so does that for small molecule drugs because of the discovery of new 'druggable targets.' I would argue that these two pathways need each other to maintain their growth in the future."

Matt Clark

President and Chief Scientific Officer, X-Chem

A world-recognized innovator and leader in the DNA-encoded library (DEL) field, Matt Clark was part of X-Chem's founding team and served as VP of chemistry and SVP of research prior to his appointment to CEO. Now operating as CSO, he has helped the company develop from a niche chemical discovery platform to a drug discovery engine. He has numerous patents and key DEL publications to his name, and previously served as director of chemistry at GlaxoSmithKline, where he led the group responsible for the design and synthesis of early-iteration DELs.

"Experimental design in the future will need to be very meticulous and robust, since systemic biases in our data streams will lead to poor predictive modeling. If we do it right, well-designed and high-throughput data flows will lead to non-intuitive predictions that can leapfrog our current paradigm of drug discovery."

J. Jean Cui

Scientific Founder, President, and CEO, BlossomHill Therapeutics

Having pioneered numerous clinical compounds, including Augtyro, Xalkori, and Lorbrena, J. Jean Cui has shown herself to be the epitome of a visionary scientist and accomplished business leader by combining a knack for therapeutic innovation with entrepreneurial expertise to design drugs and progress them to patients in need. She was elected as a Member of the National Academy of Engineering for 2024, and has won multiple awards including National Inventor of the Year and a second Pfizer Worldwide R&D Achievement Award.

"Being the person responsible for designing the molecules that become new medicines for patients is an amazing career. Using the accumulation of biology and chemistry knowledge, I am inspired to work in drug development and serve as a bridge between basic science and the treatment of patients through the creation of new molecules that address the root cause of disease."

Raquel Izumi

Chief Operations Officer, President, and Founder, Vincerx Pharma

A co-founder of several companies, Raquel Izumi has helped design and implement clinical studies, including for acalabrutinib and ibrutinib, garnering breakthrough designations, accelerated approvals, and subsequent blockbuster exits. The primary influence behind Nathan Vardi's For Blood and Money: Billionaires, Biotech and the Quest for a Blockbuster Drug, Izumi also mentors young scientists, women, and ethnic minorities. Her workforce at Vincerx comprises 44 percent women and 39 percent of employees born outside of the US.

"We have started this company (Vincerx) based on a novel modular bioconjugation platform that allows us to tailor the development of ADCs or SMDCs to address the biology of the specific cancer being targeted."

Edward Hæggström

CEO, Nanoform

A former Harvard professor with an academic portfolio consisting of over 400 papers and 25 patents/patent applications, Hæggström co-founded Nanoform in 2015 to focus on nanoparticle engineering technology for small-molecule APIs. The company's CESS technology was recently leveraged by Portuguese biotech company TargTex for a glioblastoma treatment study – and showed promising results.

"I have publicly stated that Nanoform will try to double the number of medicines that reach the market each year, with the same R&D expenditure. I was inspired by the tricorder in Star Trek and I like the idea of going where other people have not gone before."

Jerry McMahon

President and CEO, Storm Therapeutics

Author of more than 100 scientific and medical publications, and with more than 60 US patents, Jerry MacMahon has broad disease-area expertise and a specialty in oncology therapeutics. He has been an instrumental figure in the invention and development of several ground-breaking protein kinase inhibitors, including Sutent (sunitinib), and has held appointments at Yale, Tufts University School of Medicine, and MIT. He received his BS in biology and PhD in biochemistry and genetics from the Rensselaer Polytechnic Institute.

"There is a misconception that pharma is only focused on profits. I feel that there is an urgent need to educate the public on pharma being at the heart of developing new treatment options for patients, and that pharma is dedicated to medical research and the diagnosis, treatment, and prevention of diseases to improve life expectancy and quality of life for many patients."

Anders Nykjær

Founder and Chief Scientific Officer, Vesper Bio

Part of the research team that identified the Vps10p-domain receptor sortilin and its interaction with progranulin, Anders Nykjær has led several research centers that have pinpointed the sortilin receptor as a target for treating a variety of disorders, including neurodegenerative disorders. He has (co-)founded three biotech companies and is core group leader of the Danish Research Institute of Translational Neuroscience. Nykjær has also served as the Director of the Danish National Research Foundation Center of Excellence, PROMEMO, since 2017.

"Whatever you become immersed in is the most fascinating question a scientist needs to solve. It doesn't matter whether it's lipid metabolism, kidney physiology, or brain disorders; what matters is the deep dive into the unknown."

Anne Phelan

Chief Scientific Officer, BenevolentAI

Responsible for all aspects of drug discovery at BenevolentAI, Anne Phelan is passionate about building high-functioning and cohesive teams with equal gender representation that are committed to delivering life-changing medicines. With previous roles at Mission Therapeutics and Pfizer, and a BSc and PhD in Genetics from the University of Liverpool, UK, Phelan's areas of expertise range from drug discovery, molecular pharmacology, and plate based screening, to genomics, CRO outsourcing, and clinical project leadership.

"The idea that I could apply my experience in genetics and molecular pharmacology to solving some of the key unanswered questions in the most challenging human diseases, to identify drugs with the potential to directly benefit patients, is hugely motivational. It's like solving the ultimate puzzle, with a huge impact on patients' quality of life."

Mike Riley

CEO, Veranova

Mike Riley assumed the role of Veranova's CEO in May 2023, bringing more than 20 years of experience in pharmaceutical contract development and manufacturing operations. In a former role as president of Catalent's Biotherapeutics business, Riley managed a unit with more than 6,500 employees and revenue exceeding $1 billion. At Veranova, his expertise has positioned the company for sustained growth in high-potential areas. His appointments to the Veranova Scientific Advisory Board include 2022 Nobel Prize Laureate Carolyn Bertozzi.

"People need to know that you mean what you say, that you will follow through on your commitments, and that you will always seek to make the right ethical decision. Demonstrating that level of integrity in both words and actions sets the right example for your people."

Beatrice Setnik

Chief Scientific Officer, Altasciences

As well as her role at Altasciences, Beatrice Setnik also applies her expertise as an adjunct professor at the University of Toronto's Department of Pharmacology and Toxicology, where she delivers lectures and provides mentorship to aspiring students. She is also the managing director of the Cross Company Abuse Liability Council, and a member of the College on Problems of Drug Dependence, and the International Society of CNS Clinical Trial Methodology. Setnik has published numerous research articles and presented at over 200 scientific meetings and conferences. She is recognized as an expert in clinical pharmacology and abuse, physical dependence potential assessment, risk evaluations, and CNS drug development.

"Inspiring teams and mentees to take on new challenges and techniques is critical for our industry to continue to be on the innovative edge of preclinical and clinical research, as well as to lead the way in novel approaches to drug development."

Alain Beck

Senior Director, Biologics CMC and Developability, Pierre Fabre

In addition to his role at Pierre Fabre, Alain Beck is also co-founder and associate editor of mAbs – an open access journal publishing antibody research – and a member of the MabDesign founders' college. He has been involved in clinical-stage biologics R&D programs for MSD's dalotuzumab, GSK's telisotuzumab/lepatinib, and Pierre Fabre's cetuximab. He is also involved in workshops within the ANSM (France), as well as at the EMA, FDA, NIST, US Pharmacopeia, and the WHO.

Akintunde "Tunde" Bello

Senior Vice President, Head of Clinical Pharmacology, Pharmacometrics, and Bioanalysis, Bristol Myers Squibb

Tunde Bello is a member of the American Society for Clinical Pharmacology and Therapeutics, the American Association of Pharmaceutical Scientists, and the American Society for Clinical Oncology. He joined BMS in 1998, before moving to Pfizer in 2003 as clinical pharmacology group leader. He returned to BMS in 2015 and today holds key responsibilities for the development, approval, and lifecycle management of numerous marketed drugs.

"I am inspired by the progress we continue to make in the development of new medicines and therapies that are more tailored to the needs of our patients. I am also inspired by the privilege of working with talented drug developers across a wide range of functions, all working on the common goal of bringing new treatments to patients."

Piers Ingram

CEO, Hummingbird Bioscience

A mathematician by training, Piers Ingram recognized the power of bringing rational drug discovery to biologics. He co-founded Hummingbird Bioscience to fully realize the potential of emerging technologies and computational approaches for precision biotherapeutics. Recognizing the potential for ADCs with a better safety–efficacy profile, Ingram led the team to design a HER3-ADC that was recently out-licensed to Endeavor BioMedicines.

"There have been significant advances in most disease areas over the past decade, and particularly in oncology where several new modalities have made real progress. I think what underlies the success of bringing new disease insights together with new effective and safe therapies is the increasing richness of our understanding of the molecular basis of both diseases and mechanisms of toxicity, which allows us to design and optimize much more effectively."

Seth Lederman

CEO, Tonix Pharmaceuticals

Throughout his career, Seth Lederman has been a pioneer in the field of drug discovery. Currently serving as the CEO of Tonix Pharmaceuticals, he leads a team of scientists and medical professionals addressing the unmet needs of patients with painful neurological conditions, such as fibromyalgia, long COVID, and migraine. Before joining Tonix, Lederman served as a professor at Columbia University College of Physicians and Surgeons and as a rheumatologist at Columbia Presbyterian Hospital. His research in molecular immunology led to the discovery of the CD40 ligand and its role in T-cell helper function.

Hanns-Christian Mahler

CEO, ten23 health

Hanns-Christian Mahler leads ten23 health by rejecting traditional leadership attributes and styling himself as "Chief Enablement Officer" in a holacratically organized company. A pioneer for sustainability in the pharmaceutical industry, Mahler is committed to reducing the industry's environmental impact. An adjunct faculty member and lecturer at the universities of Frankfurt and Basel, he also serves as Editor for Pharmaceutical Research, Journal of Pharmaceutical Sciences, AAPS Open Journal and PDA Journal of Pharmaceutical Sciences and Technology.

"I don't like to follow general opinions and trends. I do my own research and have my own thoughts about topics. One topic that kept me going was the traditional belief that you can only administer 1–2 mL subcutaneously. In fact, you can administer much more – up to 20+ mL (even without any tissue modulating enzyme). Things like this can move the boundaries of modern treatments."

Jane Osbourn

Chief Scientific Officer, Alchemab Therapeutics

Cambridge graduate and the Crick Translational Advisory Group member Jane Osbourn was awarded an Order of the British Empire in 2019, the same year she was awarded the Scrip's Lifetime Achievement Award for services to drug discovery, development, and biotechnology. She has contributed to the development of antibody phage display technology, authored key publications and patents, and contributed to the discovery and development of antibody therapies, such as adalimumab and durvalumab.

"The generosity of patients in giving their insights, time, clinical samples, enabling assessments, and being prepared to try and help others to improve health, even if that comes with risk and inconvenience, has always inspired me."

Mahesh Karande

President and CEO, Omega Therapeutics

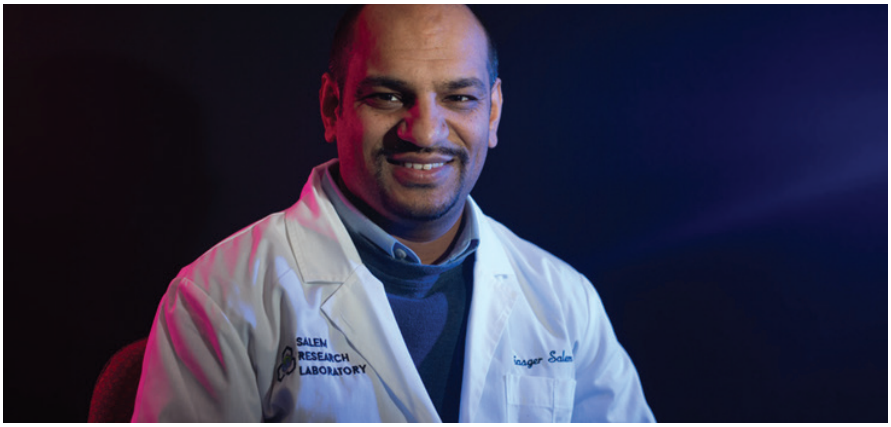
Mahesh Karande's mantra is: "What if we could target and control genes – including those that have been historically intractable – to treat and cure almost any human disease?" Under Karande's leadership, Omega has showcased the first-ever preliminary clinical data demonstrating EC-mediated pre-transcriptional control of MYC expression, a notoriously undruggable oncogene. Karande hopes to leverage his expertise and leadership to transform and expand the definition of what is achievable in biotechnology.

"In the scientific process, we inevitably run into setbacks, and it takes a balanced blend of ambition and humility to keep trying, to learn from failure, and to keep faith in the end goal. Throughout the various roles I've held during my career, and in my current position, I have always kept this ethos – ambitious, yet humble – front and center."

Mike Rea

CEO, IDEA Pharmaceuticals

A self-styled innovation protagonist/antagonist and "geek," Rea is an established author who has appeared consistently in our Power List since 2017. He is the creator of the annual Pharmaceutical Innovation Index, and also a senior fellow at FasterCures (a Milken Institute Center for accelerating medical research); an advisor with BioEthics International; strategic innovation advisor at Nanoform; advisor at OneHealth/FidoCure; and the owner and chief musical officer of Medical Records – an indie record label.



Aliasger K Salem

Associate Vice President for Research, Bighley Chair, and Professor of Pharmaceutical Sciences, University of Iowa

Aliasger K Salem's research focuses on applying nanotechnology-based approaches to improve therapeutic efficacy and reduce adverse side effects. He was the first to show that metallic nanorods could be engineered with targeting ligands and therapeutic agents in spatially defined regions, which led to the development of nanoparticles loaded with CpG and antigens as vaccines. He also developed synthetically lethal nanoparticles for treating endometrial cancer, and demonstrated that chemically modified RNA can be used to effectively regrow bone and cartilage.

"Immunotherapy breakthroughs such as immune checkpoint blockade therapies, CRISPR-Cas9 technologies that allow for gene editing and modified RNA therapies are three of the most important developments in drug discovery and development over the past decade. Drug delivery systems have been crucial to the translation of these breakthroughs into the clinic."

Paul-Peter Tak

President and CEO, Candel Therapeutics

Paul-Peter Tak is ranked among the global top 150 scientists in immunology. He has previously served as senior vice president, chief immunology officer, and global development lead at GSK, where he oversaw the creation of a portfolio of new medicines. He also co-founded Sitryx Therapeutics and led Tempero Pharmaceuticals (acquired by GSK) and Kintai Therapeutics (merged with Senda Biosciences) as CEO. Tak has brought together a world-class executive team at Candel, which recently presented proof of concept for viral immunotherapies across multiple solid tumors.

Jeff Bluestone

CEO and Co-Founder, Sonoma Bio

It took Sonoma Bio CEO and founder Jeff Bluestone 12 years to engineer a process that allowed regulatory T cells (Tregs) to propagate – a feat that doesn't even begin to cover the complex nature of Treg therapies. Under Bluestone's leadership, Sonoma Bio has grown to more than 100 employees, broken ground on a state-of-the-art Treg R&D and manufacturing facility, entered the clinic with its lead Treg therapy for rheumatoid arthritis, and forged a novel 50/50 partnership with Regeneron to discover, develop, and commercialize Treg therapies for irritable bowel disease.

"Throughout my career, I have lived by the mantra: 'do kick-ass science, collaborate like hell, and make a difference.' In this field, we're working to change the whole paradigm of how to treat devastating autoimmune diseases."

Jason Bock

CEO and Co-Founder, CTMC

An accomplished leader in innovative biologics development and commercialization, Jason Bock helped form CTMC in 2022 as a joint venture between Resilience and the MD Anderson Cancer Center to accelerate patient access to cell therapies by bridging cell therapy development and manufacturing with MD Anderson's clinical trial capabilities. Under his leadership, CTMC has successfully navigated six novel cell therapies, including Obsidian Therapeutics' TIL therapy OBX-115, and KSQ Therapeutics' CRISPR/CAS9 TIL therapy KSQ-001EX, through investigational new drug clearance in just 18 months.

"I am confident that over the coming years through both incremental and step change improvements, we will drive down the upfront costs and improve the availability of these desperately needed treatments."

Teri Foy

Senior Vice President, Cancer Immunology and Cell Therapy, Thematic Research Center, Bristol Myers Squibb

With a mission to drive leadership in cell-based therapies in hematological and solid cancers, Teri Foy and her team focus on the development and translation of BMS' early I-O and cell therapy pipeline from discovery through human proof of concept. Beyond the lab, Foy is a Healthcare Businesswomen's Association Luminary Award winner for her STEM advocacy; a leader and role model for students and women; head of BMS' Seattle R&D site; and executive sponsor of the BMS STEM Council to advance the global STEM strategy.

"It would be amazing if our team could develop a cell therapy that worked to improve outcomes for patients with solid tumors. Despite the field's success with cell therapies in blood cancers, we still have work to demonstrate that this transformative therapy can also work in solid tumors."

Fabian Gerlinghaus

CEO and Co-Founder, Cellares

Fabian Gerlinghaus is driven by a strong sense of purpose and is passionate about building the future of cell therapy manufacturing. Prior to Cellares, he was chief innovation officer at Synthego and co-invented the company's RNA synthesizer technology. His aim and vision for the future of the company is to be the de facto standard for cell therapy manufacturing.

"Redundant work across different bioprocessing and process development labs of various biotech companies, and repetition, such as repeatedly redoing process development for white blood cell enrichment, lacks value and underscores the need for standardization."

Audrey Greenberg

Chief Business Officer and Co-Founder, Center for Breakthrough Medicine (now SK pharmteco)

Beginning her career in the mid 90s in the finance sector, where she served as an investment banker for both Merrill Lynch and Morgan Stanley, Audrey Greenberg entered the pharmaceutical world in 2019. Since then, she has gone on to serve on the board for NLS Pharmaceuticals alongside her responsibilities for SK pharmeteco and the center. Her awards and honors include Most Influential Philadelphian, Healthcare Power Player, Business Journals' Woman of Distinction 2022, consecutive Titan 100 listings for 2022 and 2023, among others. Under Greenberg's leadership, the Center for Breakthrough Medicines was named the BioBuzz Maryland Employer of the Year, the Business Journals' Startup of the Year, and PHL Inno Madness champion Innovator of the Year – all in 2022.

Reshma Kewalramani

President and CEO, Vertex Pharmaceuticals

Reshma Kewalramani joined Vertex in 2017 as chief medical officer and executive vice president of global medicines development and medical affairs, becoming CEO in 2020. She has helped expand Vertex's cystic fibrosis pipeline, as well as its employee base and the number of medicines it offers. She has been named one of Fortune's Most Powerful Women, one of Boston Business Journal's "Power 50," one of Boston magazine's most influential Bostonians, and one of Business Insider's "10 People Transforming Healthcare."

Michael May

CEO, Centre for Commercialization of Regenerative Medicine

Having founded the Centre for Commercialization of Regenerative Medicine (CCRM) more than 10 years ago, Michael May has helped create a world-class organization with more than 200 employees (and over 700 alumni), as well as a center of excellence for innovation in cell and gene therapy manufacturing. CCRM is now a destination for international therapy developers to create sustainable manufacturing processes. May's success in Canada has led to the implementation of similar CCRM franchises in Australia and Sweden, worldwide collaborations with leading cell and gene therapy technology providers, and the creation of CDMO OmniaBio. Under May's guidance, CCRM has flourished to become an important voice for building effective and sustainable commercialization capabilities.

"I believe that the ecosystem is the product. That is, it doesn't matter the specific technology or company we are working on, what matters is that we are building an ecosystem. If we engineer the ecosystem, everything else falls into place."

Sheila Mikhail

Co-Founder, Asklepios BioPharmaceutical (AskBio)

Stepping down as CEO of AskBio in March 2023 to focus on her own health after encountering inequities in the diagnosis and treatment of breast cancer, Sheila Mikhail has since used her position and her voice to educate and empower women to demand more from their healthcare rights. A founder of the Columbus Children Foundation, she has helped children with free access to treatment for AADC (juvenile Parkinson's). A serial entrepreneur and philanthropist, Mikhail has a worthy repeat entrance into this year's Power List.

"While there is much excitement about gene therapies, I think that the biggest challenge facing the field is ensuring patients' accessibility to these therapies."

Phil Vanek

CTO and Partner, Gamma Biosciences

Phil Vanek has contributed to new product development with BD, Lonza, and GE Healthcare – all while supporting associations and not-for-profit entities. Vanek is an avid spokesperson for the cell and gene industry, and has contributed to international conferences and academic workshops, as both an organizer and speaker to promote the sector. He also enjoys mentoring and coaching the next generation of leaders.

"I implore all early career scientists, engineers, and innovators to think about joining this industry. It's a great industry to work in if solving highly complex multidimensional and dynamic problems appeals to your intellect, and if the opportunity to impact the well-being of people around the world appeals to your heart."

Stella Vnook

CEO, Likarda

Growing up in the former USSR, within the blast range of the Chernobyl nuclear disaster, Stella Vnook fled the bloc (via Poland, Austria, and Italy) to the US, spending the remainder of her youth in New York. Since joining Likarda, Vnook has focused on new avenues for its technology that will enable novel applications for cell and gene therapies, biologics, and traditional modalities. Likarda's platform is based on Core Shell Spherification technology, which prevents therapeutic cells and molecules from degradation, preserving biologics without ultracold freezing and storage.

"Controversies shouldn't overshadow the potential benefits of cell therapy; they should underscore the importance of careful regulation, transparent communication, and ethical decision-making in advancing the field responsibly."

the Medicine Maker

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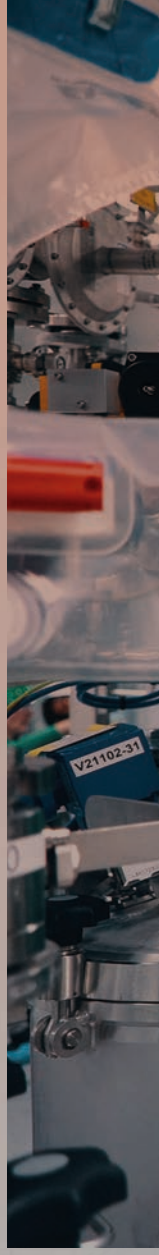
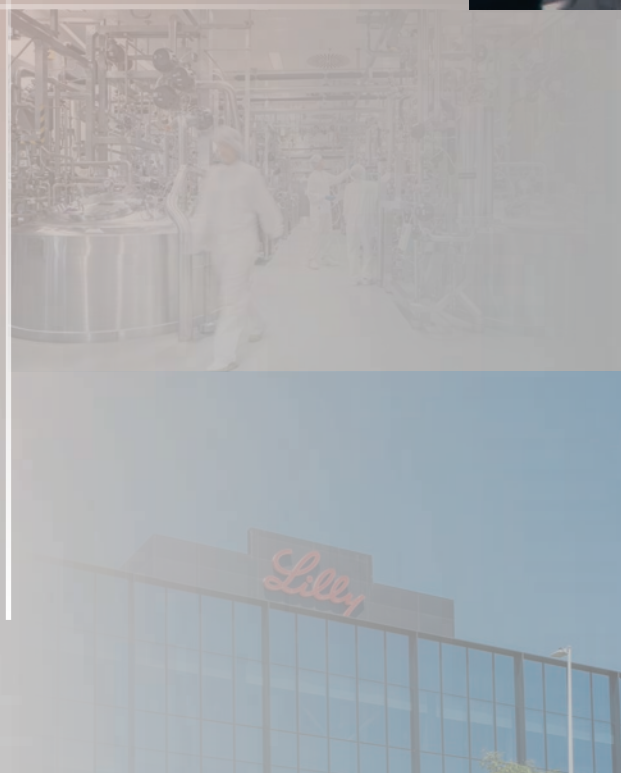
Now we move from people to companies! For the past several months, we have been asking you to vote for the top companies and service providers in the pharma industry. The results are in!





BEST BIG PHARMA COMPANY: *Novartis*

The vote here was extraordinarily close, but Novartis just edged into the lead. The company performed strongly in 2023, with a 10 percent rise in net sales, 39 percent increase in operating income, and a 62 percent rise in net income. Top selling drugs for the company include Entresto, Cosentyx, Promacta/Revolade, Kisqali, and Kesimpta.

One big strategic move for 2023 was to execute the spin-off of Sandoz. In a statement, Novartis CEO Vas Narasimhan said, "This is a truly historic moment for Novartis and Sandoz, as we begin new chapters as independent companies. With several consecutive quarters of sales growth, Sandoz starts out from a position of strength as a global leader in Generics and Biosimilars, and I am confident they are poised to deepen their impact on patients and society." He went on to describe Novartis as a "fully focused innovative medicines company… with strong financial performance and R&D momentum."

Like many of the big pharma companies, Novartis has a long history; its origins can be traced back to the 18th century. Initially, the focus was on synthetic dyes before eventually racing into chemicals and pharmaceuticals. Modern day Novartis took form in 1996 after a merger between Ciba-Geigy and Sandoz.

KEY FACTS

Global HQ:
Basel, Switzerland

Number of employees: *~76,000*

Approvals in 2023: *22 in the US, EU, Japan and China*

HONORABLE MENTION: SANOFI

BEST API AND EXCIPIENTS SUPPLIER: *Evonik*

Evonik produces specialty chemicals for a range of industries and is active in more than 100 countries. The Health Care business at Evonik provides a portfolio of functional excipients, technologies and CDMO services for oral and parenteral dosage forms for advanced drug delivery. Evonik also serves as a global CDMO for small molecule APIs, highly potent APIs, and intermediates. For biopharma customers, Evonik supplies high-quality, innovative cell culture solutions and amino acids.

Two key milestones over the past 18 months include the opening of a new facility for clinical and launch quantities of pharmaceutical lipids in Hanau, Germany and officially breaking the ground on a $220 million commercial lipid facility in Lafayette, Indiana – supported with funds from the US government. Evonik also recently started a collaboration with the University of Mainz, Germany, to commercialize a new class of PEG polymers called rPEGs, which could be of particular interest for companies working with lipid nanoparticle carriers. A recent highlight from Evonik's Drug Substance unit includes the collaboration with Phathom Pharmaceuticals to manufacture the novel acid blocker vonoprazan.

KEY FACTS

Global HQ:
Essen, Germany

Employees: *~33,000*

2023 financials:

Sales of €15.3 billion (around $16.7 billion); operating profit (adjusted EBITDA) of €1.66 billion (around $1.8 billion)

HONORABLE MENTION:
DR REDDY'S

BEST CDMO:
Boehringer Ingelheim

Drug developers are fortunate in that the pharma industry is home to many high-quality CDMOs. Votes were split amongst several companies in this category, but Boehringer Ingelheim emerged as the winner. After gaining experience from developing and launching its own biopharma products, the company created a contract services arm in 1998. Today, the CDMO business is known as Boehringer Ingelheim BioXcellence, with expertise in mammalian cell culture and microbial technologies. It has facilities in Biberach, Germany; Vienna, Austria; Shanghai, China; and Fremont, USA – with the company claiming that its Biberach site is Europe's largest multi-product mammalian cell culture plant. The Vienna and Shanghai sites were expanded in 2021, and the company was awarded "champion" status in six categories in the 2023 CDMO Leadership Awards.

HONORABLE MENTION: LONZA

KEY FACTS

Global HQ: Ingelheim, Germany

Capacity: *375 kL for cell culture and 12 kL for microbial and yeast fermentation*

2022 net sales for contract manufacturing: *~€1.02 billion euro (around $1.1 billion)*

BEST PROVIDER OF BIOPROCESSING SOLUTIONS: *Eppendorf SE*

For this category, you chose lab equipment supplier Eppendorf. Eppendorf was founded in 1945 at the University Clinic Hamburg Eppendorf to focus on improving living conditions after the war. Today, the company continues this mission by providing bioprocess solutions that help bring life-saving treatments to the world. The company facilitates life sciences research through a diverse portfolio of liquid handling and bioprocess instrumentation (including pipettes, centrifuges, mixers, ultra-freezers, bioreactors, software, and process modules), as well as consumables. The company is particularly well known for its innovation in centrifuges and describes itself as a "premium brand." Over the years it has acquired several other companies, including New Brunswick, DASGIP Group, and the centrifuge business of Koki Holdings in Japan (Himac).

Eppendorf is also active in helping to promote new talent in biomedicine, and has launched an award for young European investigators and a science prize for neurobiology.

KEY FACTS

Global HQ:
Hamburg, Germany

Number of employees: >5000

HONORABLE MENTION:
THERMO FISHER SCIENTIFIC

BEST PROCESSING EQUIPMENT COMPANY

L.B. Bohle

Granulation, milling, sieving, blending, tableting, containment, continuous manufacturing and more – L.B. Bohle offers equipment for many aspects of traditional pharmaceutical manufacturing, including both laboratory and commercial scale systems. The company was founded in 1981 by Lorenz Bohle. Today, the company is recognized worldwide as a technology leader in tablet manufacturing processes. With subsidiaries in the USA, India and Switzerland, L.B. Bohle has a global presence. Recently, L.B. Bohle launched its new product generation with the BFC 400 tablet coater, the BRC 100 dry granulator and the QbCon 1. More machines will follow this year.

KEY FACTS

Global HQ: Ennigerloh/ Westphalia, Germany

Production area: *40,000 m2*

HONORABLE MENTION: THERMO FISHER SCIENTIFIC

BEST PACKAGING SPECIALIST

Schott Pharma

This is a new category for 2024. And you voted for Schott Pharma – and its portfolio packed with prefillable syringes, cartridges, vials, ampoules, analytical development services, and other solutions in containment and drug delivery. On average, more than 25,000 patients every minute receive an injection stored in a Schott Pharma product. The company manufactures solutions made out of borosilicate glass or high-grade pharmaceutical COC polymer. In 2022, Schott Pharma was carved-out from Schott AG – which dates back more than 130 years – to when Otto Schott set out to innovate in the world of glass.

In September 2023, the company made its debut on the Frankfurt stock exchange. And 2024 started with a bang for the company; in January, the company released its first sustainability report, launched a new range of vials for deep-cold temperature applications like mRNA and gene therapy, and reported 2023 revenues up by 9 percent compared with the previous year.

HONORABLE MENTION: BD

KEY FACTS

Global HQ:	Mainz, Germany
Number of employees:	*~4600*
Fiscal year 2023 financials:	*€899 million ($976 million; fiscal year runs from October to September)*

BIGGEST TALKING POINT

Eli Lilly

A big talking point of 2023 was the use of monoclonal antibodies against Alzheimer's disease. Biogen and Eisai's aducanumab failed to generate excitement, but lecanemab is a different story. There are still concerns about how successful it will prove to be, but it has certainly shown that new advancements in drug development for Alzheimer's are possible.

Enter Eli Lilly with its own anti-amyloid monoclonal – donanemab – that has been garnering significant attention since positive phase III results in 2023, with many believing that it could be even more effective than lecanemab. A statement from Eli Lilly in 2023 said, "This is the first Phase 3 trial of any investigational medicine for Alzheimer's disease to deliver 35 percent slowing of clinical and functional decline."

Unfortunately, the company was in the headlines again when its bid for accelerated approval from the FDA was rejected in January 2023 because of the limited number of patients with at least 12 months drug exposure. Lilly has since filed a new submission with the FDA – and a decision is expected later in 2024.

The year 2023 was actually a somewhat tough one for Lilly, which also received two other rejections from the FDA – although these were for deficiencies at a third-party contract manufacturer rather than issues with the drug itself.

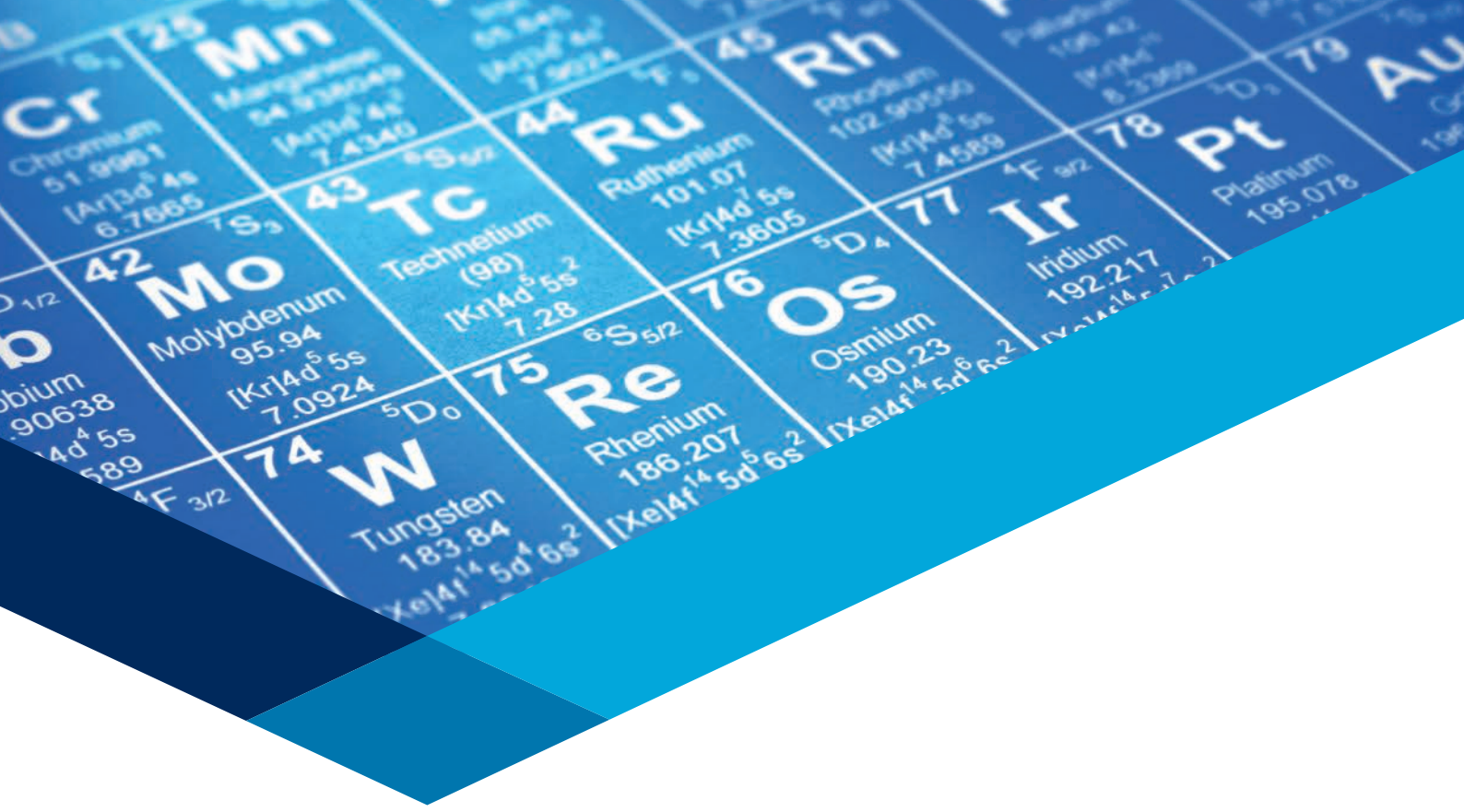
Full year revenue for 2023 was not available at the time of publication, but the company reported 2023 Q4 revenues as rising by 28 percent compared with the same quarter the previous year.

KEY FACTS

Global HQ:
Indianapolis, USA

Number of employees: ~ 42,000

HONORABLE MENTION: VERTEX PHARMACEUTICALS & CRISPR THERAPEUTICS



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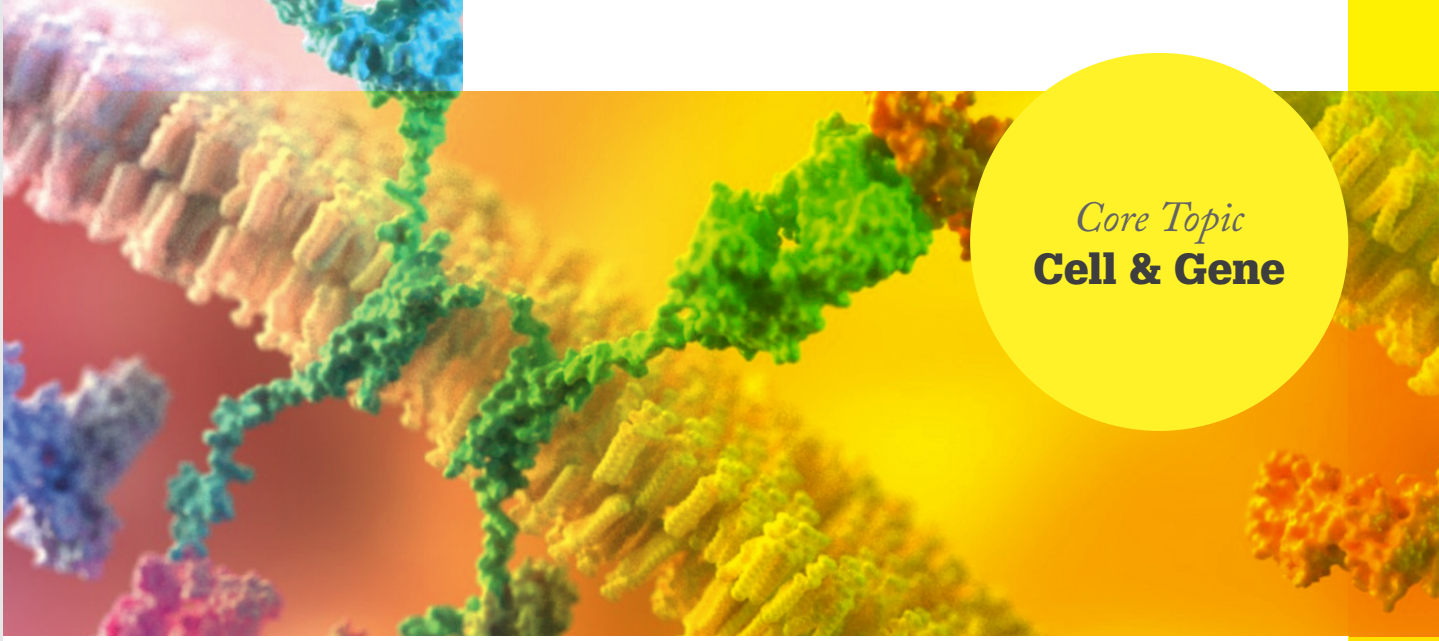

Credit: Shutterstock

Core Topic
Cell & Gene

To boldly go. Oculogenex will be using the International Space Station to test its investigational gene therapy for preventing and potentially reversing vision loss from age-related macular degeneration (AMD). The therapy has been shown to be effective in models of retina degeneration, but these models don't emulate intermediate AMD. The space mission aims to "validate spaceflight as a novel biologic model of intermediate AMD" and assess if the therapy can "thwart spaceflight-induced retinal dysfunction and degeneration."

For the elderly. Many patients over the age of 65 with acute myeloid leukemia are considered too infirm for treatment using allogeneic hematopoietic stem cell transplant (allo-HCT). However, a new study shows that outcomes for these patients have improved since 2000 thanks to advances in care, new antiinfectives, and high-res human leukocyte antigen typing. "In tandem with the marked increase in elderly patients receiving allo-HCT, we observed an impressive improvement over time in leukemia-free and overall survival," explained senior author of the study, Ali Bazarbachi. "These data indicate that allo-HCT should no longer be optional but should be mandatory for elderly patients."

A big pricetag. Orchard Therapeutics has received FDA approval for Lenmeldy to treat children with metachromatic leukodystrophy (MLD). The 37 children receiving the treatment in two open-label clinical trials had a significantly reduced risk of severe motor impairment or death compared with untreated children. However, the therapy's price tag of $4.25 million has drawn criticism. It will be the most expensive drug in the US. Frank Thomas, president and chief operating officer of Orchard Therapeutics, said: "We are confident in the potential long-term clinical outcomes of Lenmeldy and will continue to work with public and private payers to structure outcomes-based and other types of innovative reimbursement models that appropriately balance the needs of patients and families for adequate access, health care systems for affordability, as well as support future research and development of treatments for ultra-rare diseases like MLD."

Not so nice roadblock. At the back end of 2023, the UK became the first country in the world to approve the gene edited therapy Casgevy for sickle cell disease. However, in draft guidance, the country's cost watchdog NICE has said it does not recommend the drug for use on the country's National Health Service. The NICE committee acknowledged that only a small number of patients would require treatment and that Casgevy could offer a cure to a larger population. However, they noted that further data collection on the therapy's effectiveness and a potential commercial arrangement would be needed.

IN OTHER NEWS

Sarcura secures €1.7 million research grant from Austrian Research Promotion Agency to accelerate miniaturized and autonomous cell therapy manufacturing platform

Nature study (10.1038/s41375-024-02220-y) suggests closed-loop manufacturing of CD22-CAR T cells associated with favorable safety profile in children and adults with B-cell acute lymphoblastic leukemia

ReciBioPharm to collaborate with GeneVentiv Therapeutics on development of AAV-based universal gene therapy for hemophilia

UK National Institute for Health and Care Research announces £17.9 million in funding to support clinical trials for advanced therapy products

Janssen's CAR T Carvykti receives recommendation from FDA advisory committee for use as earlier line of treatment for adults

May the Outsource Be With You

Experts suggest that outsourcing CGT manufacturing capabilities to CDMOs brings additional benefits, although not without challenges

By Nandu Deorkar, Senior Vice President, Research & Development, and Greg Swan, Business Development, Cell and Gene, both at Avantor

The breadth and availability of cell and gene therapies (CGTs) is advancing at a historic pace as more of these treatments move from research to full-scale manufacturing. Though FDA-approved CGTs represent only a small fraction of conventional drugs, the forecasted growth rates are staggering. Sales of conventional drugs and non-CGT biologics are expected to achieve five percent compound annual growth rate (CAGR) from 2022 to 2028, while CGTs are forecasted to achieve a CAGR of up to 46 percent, an estimated $86 billion in sales, by 2028. (1)

It's an exciting but also challenging time. The high expense of manufacturing these therapies stresses the economic viability of scaling to commercial production and broad clinical usage. To solve these cost and scaling issues, we will need to address many technical, quality, and logistical issues – including a lack of manufacturing capacity and regulatory adherence.

One solution that has risen to the top for CGT companies, small and large, is outsourcing development and manufacturing. CDMOs have specialized manufacturing knowledge, as well as the right infrastructure and quality control processes – and the option is always open for customers to bring manufacturing back in house.

Here, we discuss what we believe to be some of the key advantages that outsourcing can bring to cell and gene therapy development.

The raw material benefits

Manufacturing workflows for cell and gene therapies increasingly require specialized lipids, proteins, and reagents that are not related to traditional therapeutic modalities. With the importance of cost efficiency clear, chemical and single-use providers are receiving more and more requests for cGMP grades of materials that previously were not needed at scale or to cGMP specifications. As CDMOs often manage several sponsor projects, their scale can drive collaboration with providers to develop new materials and to implement improvements in raw material inputs – balancing the additional costs of cGMP grade raw materials with potential savings in time and labor.

Although there is considerable raw material expense associated with some components, such as plasmid DNA, transfection reagents, and enzymes (2), the greater danger lies in changing any materials at a late stage in clinical development. Late changes can result in batch failure or process variability, leading to delays and added expense. In addition, cell and gene therapies are more sensitive to degradation than other modalities. In the case of cellular therapies, biological activity must be retained, which limits the use of harsh purification methods. This special sensitivity requires raw materials that meet critical performance specifications from the supplier, so potentially harmful or adventitious agents are kept out of the supply chain. Reliable access to materials of the correct analytical grade is, therefore, more critical than ever before to overcome potential supply bottlenecks. Working with material suppliers during CGT therapeutic process development and using external suppliers for hydration management and other customized materials allows for greater portability of therapeutic manufacturing to other partners and global manufacturing sites.

To do this effectively, choosing a globally established material supplier is best, because they will likely offer necessary redundancies and supply chain security, such as multiple sites qualified for materials, access to new sources of materials, and the ability to hold inventory in strategic locations. CDMOs are also very good at choosing the right material suppliers.

Efficiencies in manufacturability

If cell and gene therapies are to become widely used across the population, innovation in process technology is essential. Process standardization has helped other biologics, such as monoclonal antibodies, advance – increasing recoveries consistently

to 90 percent or more (3). In cell and gene, making the leap to standardized production systems in downstream workflows, through a platform approach, can also improve yields at scale. This gain in efficiency has been seen across the CDMO industry with flexible platforms being marketed in the viral vector space. But furthermore, outsourcing with a contractor that is both a materials and single-use manufacturer provides additional guidance on where to adopt technical, quality, and regulatory best practices from more established therapies.

Implementing closed and automated systems can lead to significant process improvements and help eliminate risk. Any manual operation represents a significant failure mode and could be overcome with a custom-designed process using a closed system. Vector propagation, purification, and cell line optimization are additional examples of steps that need improvement. Here, an effective partner that has a solid understanding of the contribution of labor, overheads, and possible economies of scale from reducing processes will be able to help accelerate development.

In a constantly changing landscape, large biopharmaceutical manufacturers producing traditional therapies have a deep bench of experts to optimize workflows in several important areas, including process engineering, production chemicals and excipients, and single-use technologies. In the cell and gene space, expertise is still limited. Many of the companies developing these therapeutics are small to medium size (4), making them more likely to benefit from the expertise of a service provider.

To invest in infrastructure – or not

Internal manufacturing of biologics requires a substantial investment that can tie up capital for years before a return is realized – if the product makes it to market. The specialized manufacturing facility itself, high-end equipment, procurement, and warehousing of consumables, and specially trained and qualified employees, require an enormous amount of cash to establish.

Large pharma with established facilities can often re-purpose manufacturing capacity to new trial therapeutics and are more insulated from single candidate trial failures. On the other hand, many new cell and gene companies have no or few therapeutics on the market. Additionally, as these therapeutics pipelines are likely in an early phase and the performance of the candidates is uncertain, there are many unknowns regarding the size of manufacturing space needed. When considered with the high turnover of company acquisition and dissolution, individual investment in large-scale manufacturing facilities may be seen as nonviable for many players in the cell and gene space.

To meet the need of companies with investigational pipelines, some CDMOs specialize in single-batch, rapid production of therapeutic candidates and have specialized scaling methodologies. For late phase and commercial production, other CDMOs offer reserved suites for long-term manufacturing.

However, there has also been recent examples of companies with on-the-market cell and gene therapeutics bringing manufacturing back in-house. This is likely due to the desire to further control quality in-house and that the need to regularly produce the same therapeutic significantly reduces the financial risk of investment into specialized manufacturing facilities. Further, the mentioned benefits of having, and paying for, an external manufacturer may, in some instances, fade as processes are firmly established and optimized, while the benefit of having complete control of production timelines to meet consumer demand increases. In other circumstances, some companies may also need to move their therapeutic from one CDMO to another. If companies rely solely on their CDMO partner for all development, material handling, and preparation, they may experience significant delays and challenges when shifting manufacturing bases. In this case, it may be more effective to partner with an independent service provider/material supplier that can service both the therapeutic developer and the CDMO manufacturer.

It is certainly an exciting time for the cell and gene therapy field – with many therapeutics in trials using a plethora of technologies and being developed by an innovative, young pharma sector. With rapidly evolving pipelines that are predominately pre-revenue, these cell and gene companies are better equipped to expend resources on therapeutic development rather than take on the challenges associated with clinical trials and commercial-scale manufacturing. This phase is resource intensive and has a concerted focus on staffing with experienced production engineers.

Outsourcing to experienced manufacturers and chemical/material suppliers that can better implement workflow technologies and quality standards is an effective option. In our view, collaboration between independent manufacturers, suppliers, and therapeutic inventors will be key to driving down cost reduction and increasing global market access.

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Core Topic
Bioprocessing

Biosimilar boom. It's been a productive month for Sandoz. The company has acquired the Cimerli business from Coherus for an upfront cash payment of $170 million. Cimerli is a biosimilar to ranibizumab and is interchangeable with Lucentis for all approved indications. Sandoz has also recently received FDA approval for its denosumab biosimilars Wyost and Jubbonti, including interchangeability status with the reference medicines Xgeva and Prolia (manufactured by Amgen). The biosimilars have the same dosage form, route of administration, dosing regimen and presentation as the respective reference medicines. However, Sandoz has yet to commit to an anticipated launch date because of ongoing litigation with Amgen.

Chinese biotech ban. A US Senate committee is pushing forward with the US Biosecure Act, which will ban Chinese biotechnology firms from US federal funding, including contracts. The Act specifically mentions certain Chinese companies, including BGI Genomics and WuXi AppTec. The Act won't prevent US companies from partnering with Chinese companies, but any companies with Chinese partners will also be barred from federal contracts. The legislation has been backed by the Biotechnology Innovation Organization, which also added that it is "taking steps to separate from Wuxi-Apptec."

Tentacle-inspired R&D. Abbvie and Tentarix have agreed a collaboration to develop multifunctional biologics in oncology and immunology using the Tentarix Tentacles platform. The platform can produce "multi-functional, conditionally-active antibody-based biologics that are designed specifically to activate immune cells that can modulate disease pathways, while potentially mitigating safety concerns associated with non-specific targeting of other immune cells." The platform uses different technologies to understand cell surface proteomes, discover "tentacle" components, and conduct screening. Tentarix will receive an upfront payment of $64 million from Abbvie.

Pig pharma. Rensselaer Polytechnic Institute researchers have developed synthetic heparin in the lab, and a potential biomanufacturing process for the widely used anticoagulant that could bring about the end of its extraction from pig intestines. Jonathan Dordick, Institute Professor of Chemical and Biological Engineering, and vice president of Strategic Alliances and Translation, said: "Our goal was to find an alternative to a drug that's been on the market since 1935. For a private company, that kind of project would bring too much risk. But a university, especially one like RPI, is the perfect place to pursue this kind of project." The study has been published in PNAS (DOI: 10.1073/pnas.2315586121).

IN OTHER NEWS

Polyplus receives GMP accreditation from Belgian federal agency for medicines and health product for plasmid DNA production at Xpress BIologics Milmort facility

SK bioscience breaks ground on vaccine manufacturing plant L HOUSE in Gyeongsangbuk-do; facility will be used for producing pneumococcal conjugate vaccine candidate with Sanofi

Waters introduces data bridge to connect liquid chromatography systems and multi-angle light-scattering instruments for large molecule characterization

Process development and cGMP manufacturing completed at Lonza's Slough UK site in less than 10 months for Epsoliogen's immunoglobulin E drug candidate MOv18

Fibrocor Therapeutics agrees research development collaboration with McQuade Center for Strategic Research and Development

Four Thoughts: Single-Use Technologies

A quick look at trends in single use – plus top tips for making the switch

Timothy Korwan, Director of Technical Applications at Avantor

The trends

Single-use technologies are now an integral part of the bioprocessing manufacturing landscape – and we continue to see rapid growth in this area with the development of new components and processes. Single-use fluid pathways offer significant manufacturing flexibility and process efficiency for multiple biopharma modalities, but this doesn't mean that everything is perfect. End users should continue to evaluate their processes for areas of improvement.

The biggest trend today continues to be identifying and removing vulnerabilities in the global single-use supply chain. The COVID-19 pandemic highlighted many challenges, and companies are now working to establish primary, secondary and, in some cases, tertiary suppliers for single-use components. The need for supply assurance isn't limited to re-evaluating existing finished products, and any new designs that are created are undergoing scrutiny to understand at the component level where dual supply or equivalency can be gained to increase confidence in the supply chain.

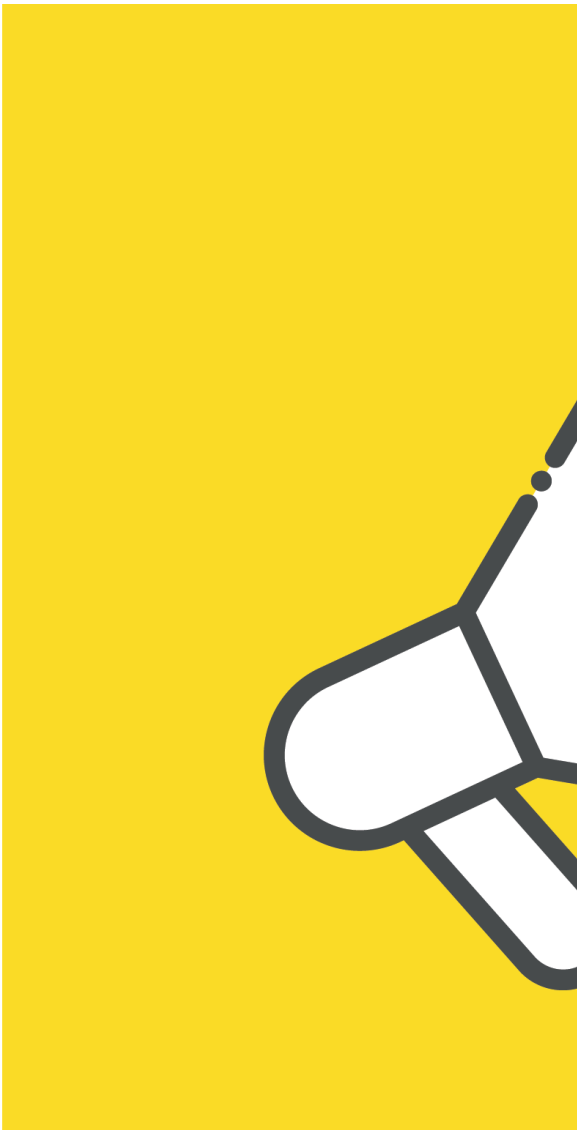
The switch

Single-use isn't right for every company or every manufacturing situation. Stainless steel may be preferred because of material compatibility or process conditions such as temperature, pressure or process volumes that exceed the limitations of polymeric single use systems.

If you want to make the switch to single-use, you must closely review the type of technology available, including connectors, tubing, filters, and so on. Also, spend time evaluating about your vendor selection. Do you want to use one vendor or multiple vendors? To be successful with single-use technology, you must ensure proper management of your single-use supply chain and be able to harmonize this with demand.

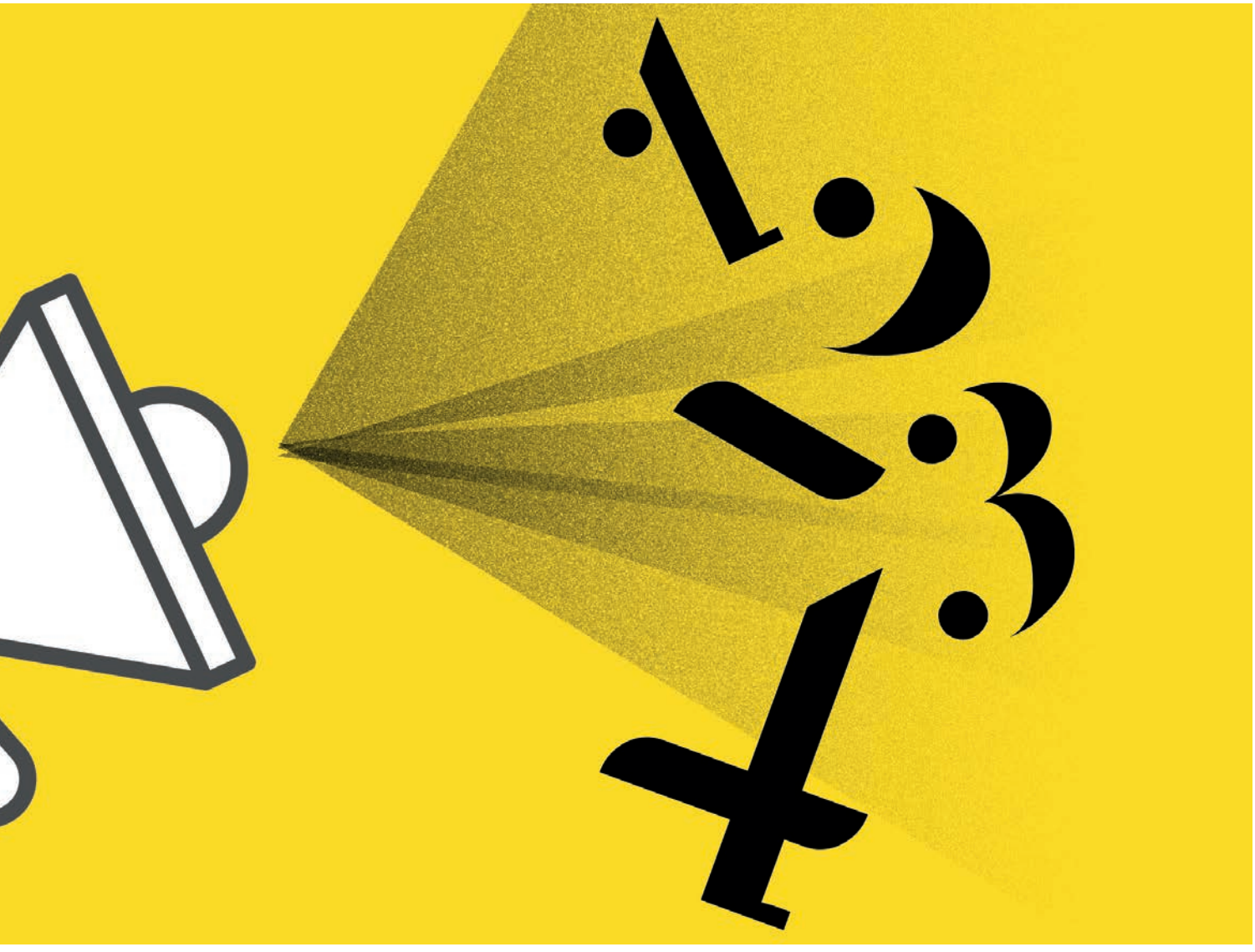
You must also consider quality and regulatory requirements, of course. Ensuring your supplier's regulatory compliance program includes sterility and that their packaging claims are in alignment with your expectations will help avoid unnecessary disruption to implementation. Particulate control is of utmost importance and understanding the environmental monitoring system being used during single-use manufacturing is a critical quality attribute. It's equally important to understand the corrective action process and align your expectations with that of your supplier.

"The COVID-19 pandemic highlighted many challenges, and companies are now working to establish primary, secondary and, in some cases, tertiary suppliers for single-use components."



The mistakes

Mistakes do happen when changing to single-use. Many mistakes often begin at the design phase of the product life cycle. The raw material or component



selection is critical to the overall health of the product life cycle, so as your process continues to scale in volume and size, ensuring your single-use technology and associated equipment can scale with your process is critical.

Too often, unsuitable technology results in an inability to scale due to supply constraints, which causes unnecessary revalidation or stock out situations at commercialization. Creating single-use fluid pathways based on a specification and creating redundancy will build in flexibility if a change is required. Further, accounting for assurance at the design phase of your process can assure greater success with scale.

The future

I see more companies adopting single use in the future, and new technologies will add even more benefits. For example, AI technology is already being implemented to better manage the single-use supply chain. Monitoring inventory levels, automated buying and restocking of shelves will help alleviate the strain and avoid costly stock out situations. Quality monitoring systems for automated quality control and vision systems will also improve product quality.

Finally, sustainability is also of great importance; material advances will continue to progress and the increased use of sustainable and/or recyclable materials will become more common practice.

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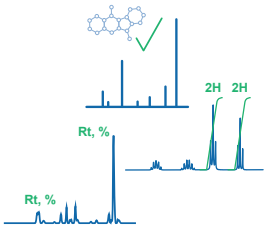
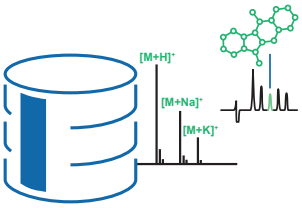


Contextual data storage



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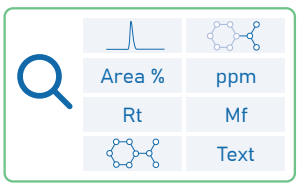

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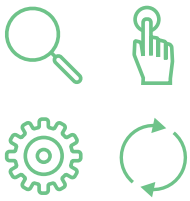

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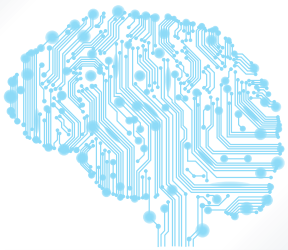
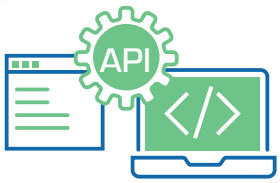


Harmonized, AI/ML-ready data



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Core Topic

Small Molecule Manufacture

Anti-COVID. Research published in the Journal of Medical Virology (DOI: 10.1002/jmv.29507) suggests that antibiotics can target gut bacteria that harbor the virus that causes COVID-19. 211 subjects – both vaccinated and unvaccinated – were studied, and those given early antibiotics treatment recovered more quickly than those who didn't. The efficacy of certain antibiotics in infected cultures had been evaluated in the lab, with promising results in the clinic through the use of a combination of amoxicillin and rifaximin within the first three days of contracting COVID-19, which also appeared to prevent any symptoms of long COVID.

Generic guidance. The FDA has developed a final guidance for the industry, which will provide process information for generic drug manufacturers on the submission of controlled correspondence to and from the FDA. Titled "Controlled Correspondence Related to Generic Drug Development," the new guidelines replace the 2020 counterpart of the same title and will describe the process by which generic drug manufacturers can submit clarification requests to clarify ambiguities in FDA's controlled correspondence response and the Agency's process for responding to those requests.

Another win for aspirin? A study published in JAMA suggests that aspirin for metabolic dysfunction-associated steatotic liver disease (MASLD) could reduce the quantity of hepatic fat at six-month follow-up compared with placebo (DOI: 10.1001/jama.2024.1215). The preliminary findings show that aspirin may reduce the severity of MASLD, and the incidence of end-stage liver disease and hepatocellular carcinoma. However, the effect of aspirin on MASLD is unknown. Researchers from Boston, Dallas, and San Diego will continue to test whether low-dose aspirin reduces liver fat content, compared with placebo.

Obeldesivir against ebola. An early study from the Galveston National Laboratory (based at the University of Texas) and Gilead has concluded that obeldesivir could have benefits in postexposure prophylaxis and treatment of filovirus infections, including Sudan ebolavirus. Obeldesivir has shown potential use in the management of filovirus outbreaks through the rapid treatment of contacts (and contacts of contacts) of known exposures, breaking the chain of transmission and better containing an outbreak. Obeldesivir was originally an oral COVID-19 antiviral drug that failed to meet its primary endpoints in clinical trials, but the company has been exploring alternative applications.

IN OTHER NEWS

Hovione and GEA partnership launches ConsiGma CDC flex Continuous Tableting Technology, and installs lab-scale R&D rig in Portugal

Galimedix announces encouraging data with orally available small molecule GAL-201 showing symptomatic alleviation potential in Alzheimer's

Santhera launches Agamree (vamorolone) for treatment of Duchenne muscular dystrophy in the US through Catalyst Pharmaceuticals

Roquette agrees acquisition of New York-based IFF Pharma Solutions to expand pharmaceutical product range

Corealis Pharma completes expansion of labs ahead of schedule; now due to be operational by end of Q2 2024

Capsules: Make Way for Pastillation

It's already used for processing powders in many industries; here's why pastillation should come to pharma next

By Subhashis Chakraborty, General Manager – Head Global Product Management at ACG Capsules

Used in chemical engineering, pastillation has a long history of transforming powders – which are difficult to work with – into solid, uniform pastilles. This makes the compounds easier to use and, in many cases, safer to handle. As an outcome of the melting process, the resulting pastilles are robust and extremely versatile. Today, pastillation is used across multiple manufacturing sectors including chemical, plastic and food.

Although my PhD research recognized pastillation as a potential process to advance drug delivery (1), it has yet to be fully explored by the pharmaceutical sector. Over the course of five points, I'd like to describe how it could be a game-changing process for the industry.

First, improving oral drug delivery. Pastillation technology has the capacity to create unique hemispherical shaped pastilles in a variety of colours which, when filled into transparent capsules, can differentiate one capsule from another. This not only improves the aesthetics of the dosage form, but also reinforces brand recognition and enhances their marketability. This presents a great opportunity for product lifecycle management, especially for products with poor market presence. The vibrant blend of colours and their aesthetic appeal can also overcome the perception of consuming medicines and thus improve overall patient acceptability and compliance.

Second, manipulating release profiles. Another interesting aspect of pastillation is its ability to generate different drug release profiles, including immediate, sustained, or even a combination of both. The drug release profiles are based entirely on the physio-chemical properties of the excipients used as the base for drug delivery. For example, water-soluble, high molecular weight polyethylene glycols (PEGs) are suitable for immediate release, while a variety of water-insoluble solid lipids are suitable for sustained release. When these excipients and the APIs are heated together to form a homogeneous melt, the drug either solubilizes or disperses depending on its physio-chemical behavior. The two types of pastilles obtained can then be filled separately or in the same capsule. Alternatively, pastilles can be formulated using both types of excipients together to customize the drug release as required.

Third, decreasing the quantity of APIs needed. It is well known that if an API melts or dissolves, it turns from a particulate to a molecular state, leading to an exponential increase in surface area. This enhances solubility, helping with quick dissolution, improving permeability, and significantly reducing the barriers for absorption in the body. The increased solubility and permeability offer the potential to reduce the dose

of APIs which, in turn, creates an opportunity to minimize adverse effects. Fortunately, pastillation technology provides an avenue to develop drug products with improved solubility and permeability.

Fourth, pastillation is suitable for highly potent APIs (HPAPIs). It is crucial to develop a rigorous and detailed plan for the safe handling of highly potent actives, minimizing direct worker exposure and ensuring the safe management of resulting waste materials to minimize environmental impact. Pastillation provides an excellent method for formulating drug products containing HPAPIs because it involves immediate conversion of powders into melt, resulting in a dust-free process.

Fifth, pastillation technology is also deemed to be an in-line process. Pastillation involves the sequential process of mixing excipients and API, melting, creating pastilles, cooling, capsule-filling and seamlessly progressing to bottling/blistering and packaging without interruption. Continuous manufacturing of pharmaceutical products on a single, uninterrupted production line is highly encouraged by the FDA – largely because it results in minimal human interventions, thus reducing the possibility of errors.

"Pastillation involves the sequential process of mixing excipients and API, melting, creating pastilles, cooling, capsule-filling and seamlessly progressing to bottling/blistering and packaging without interruption."

Naturally, there are challenges that need to be overcome for pastillation to become widely used in the formulation of pharmaceuticals and nutraceuticals. Introducing a new product which then needs to go through the entire drug development cycle requires a large upfront investment, coupled with dedicated equipment. Not all companies want to change their manufacturing set up for a new technology. I'd envisage start-up companies looking to 'disrupt' the status quo exploring this technology. For example, well-funded entrepreneurs who are looking to introduce novel dosage forms into the market – especially in areas where dose reduction coupled with sustained release is required.

For now, however, I think it is most likely that we will see pastillation be tested in the nutraceuticals and healthcare segments, where it is easier to launch than the more regulated pharmaceutical markets. The pharmaceutical sector may then have visibility of the technique's progress and successes – and see the benefits it can offer in product differentiation.

Entering the healthcare and pharmaceutical markets with new technologies and processes is not always an easy journey. To reach their full potential and find success, new methods need to prove their value and worth. With its ability to differentiate drugs, improve marketability, and enhance oral drug delivery, I believe pastillation has the potential to be one such technology. Already successful across a wide range of manufacturing sectors, it can save time and money, reduce errors, and simplify production. We're already seeing the industry look to emerging areas, such as nanotechnology, for formulation advances, so why not look at pastillation which is a far simpler and safer process?

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Clinical Trials: How Far We've Come

And yet how far we still have to go…

By Claude Price, VP & Global Head of Clinical Data Management at Quanticate

Let's start with the good news. Over the last decade, clinical trials have undergone significant improvements, driven by advancements in technology, changes in regulatory guidelines, and increased recognition of the benefits of a patient-centric approach. Here are five key examples of progress in clinical trials:

Digitalization of clinical data management. Global acceptance of electronic data capture (EDC) systems and electronic health records (EHRs) has streamlined data collection and management, making trials more efficient and reducing errors associated with paper-based processes. This digitalization enables real-time data analysis and facilitates remote monitoring, improving trial oversight, and patient safety.

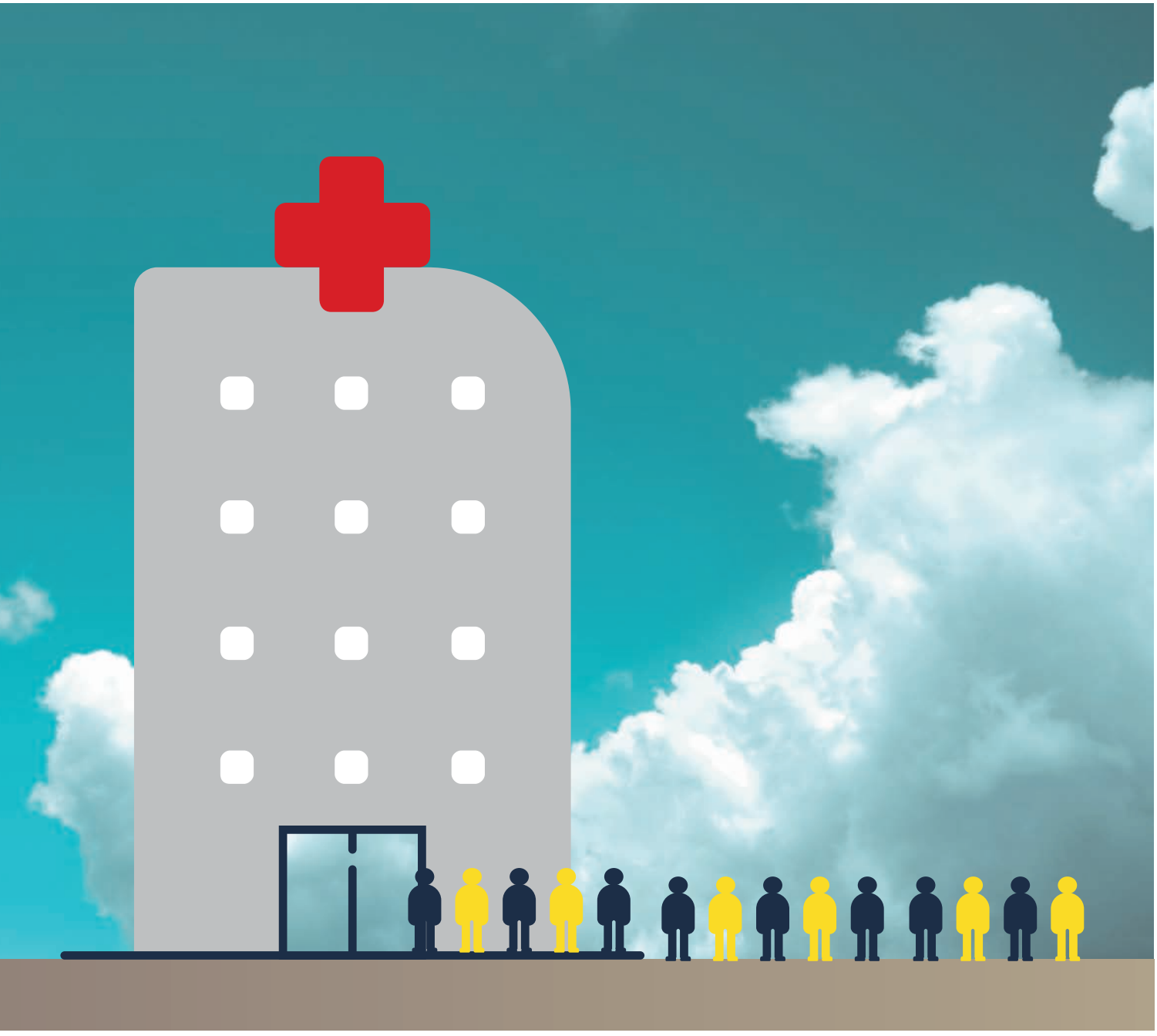
Adaptive trial designs. Adaptive trial designs allow for modifications to the trial protocol based on accumulating data, which enhances efficiency by allowing adjustments to sample sizes, treatment arms, or endpoints during the trial, increasing the likelihood of successful outcomes. Adaptive designs also help accelerate the identification of promising therapies or the termination of ineffective ones.

Patient engagement and inclusion. Patient engagement strategies aim to incorporate patient perspectives and preferences, ensuring that trials are more relevant, accessible, acceptable to participants and improve patient care. This involvement leads to higher retention rates, improved patient compliance, and more meaningful outcomes.

Decentralized and remote trials. The COVID-19 pandemic accelerated the adoption of decentralized and remote trial models. These approaches leverage telemedicine, remote monitoring devices, and mobile health applications to reduce the need for patients to visit physical trial sites, making participation more convenient and inclusive. Remote trials have the potential to increase patient enrollment, diversify participant demographics, and enhance data collection.

Real-world evidence (RWE). Real-world data (RWD) and RWE are being increasingly used to supplement traditional clinical trial data. RWD is collected from various sources, such as electronic health records, wearable devices, and patient registries. By integrating RWD into clinical trials, researchers can gather additional insights into treatment effectiveness, safety, and long-term outcomes, improving the understanding of a therapy's real-world impact.

The bad news? Running efficient and cost-effective trials is still challenging. Clinical trials are complex – and the more complex the trial design, the more difficulties a company may face in designing and selecting appropriate endpoints. Defining clinically meaningful and statistically robust endpoints that align with regulatory requirements and patient



perspectives will always be a challenge. Additionally, adaptive trial designs, while advantageous, can introduce additional complexities in trial planning and execution – and these types of trials are increasing across the industry. However, this latter challenge can be mitigated by using skilled biostatisticians with experience in complex trial types.

The participation challenge

One challenge that is a hallmark of clinical trials is enrolling sufficient participants within the required timeframe. Recruitment difficulties can lead to delays, increased costs, and a lack of diversity in the study population. This is especially true in rare disease trials, where patients that meet trial entry criteria are few and far between. In a traditional clinical trial, you may have to set up multiple trial sites for very few patients, which increases the cost of the trial. Here, decentralized trial approaches can help by allowing patients to enroll from around the globe, with less reliance on physical trial site locations.

Though decentralized trials (also known as virtual trials or remote

Save the Date

International Clinical Trials Day is celebrated annually on May 20. The aim is to highlight the vital role that clinical trials play in the development and evaluation of new treatments, therapies, and medical interventions. It aims to educate the public about the purpose, process, and benefits of clinical trials. The day serves as an opportunity to recognize the contributions of clinical trial participants, researchers, healthcare professionals, and advocates who work tirelessly to conduct and support clinical research. The day also serves as a platform to acknowledge the patients who volunteer to participate in clinical trials. Their commitment and willingness to contribute to medical progress are recognized and appreciated. Their participation helps researchers gather valuable data, test the safety and efficacy of investigational treatments, and ultimately improve patient outcomes.

trials) offer advantages in terms of convenience, patient participation, and data collection as noted above, not all trials are suitable for this approach. Various factors determine the potential for virtual visits, including the nature of the trial, therapeutic interventions, data collection requirements, and the patient population. Trials suitable for virtual trials may include observational studies, non-invasive interventions, chronic disease management, post-marketing surveillance, and patient-reported outcomes research.

On the other hand, trials that will require in person visits are likely to be interventional trials, phase I safety studies, or imaging or biomarker assessments. Vulnerable or high-risk populations also benefit more from in-person trials.

It's important to note that deciding to conduct a trial virtually or require in-person visits depends on carefully considering the specific trial objectives, participant characteristics, regulatory requirements, and available technologies. Hybrid approaches that combine virtual and in-person elements may also be used to strike a balance between convenience and the need for physical interactions.

The digital age

Despite advances in data management for clinical trials, data integrity can also be a significant challenge. Clinical trials generate vast amounts of data, which must be managed and integrated across multiple sites, systems, and stakeholders. Ensuring data quality, standardization, and interoperability are crucial for meaningful analysis and interpretation – and to avoid fraudulent data.

In my view, one of the most important changes in clinical trials is digitalization. EDC is today the minimum standard for clinical trials and data collection, but we can do even better by adopting newer technologies such as electronic clinical outcome assessment (eCOA). eCOA systems enhance the collection of clinical data outside of traditional research sites and improve data quality through the use of smartphones, tablets, or wearables – either provided to patients or used on their own devices in a "bring your own device" trial.

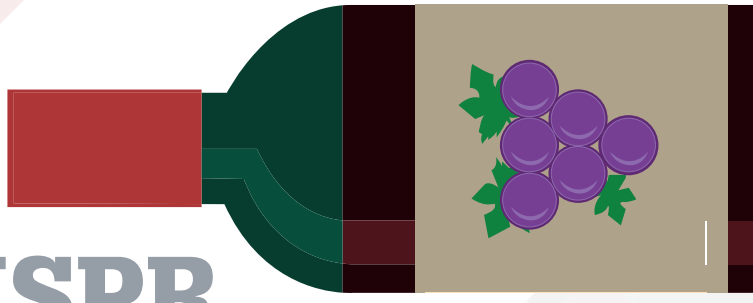
Even with rigorous statistical planning and adaptive trial designs, clinical trials have a level of uncertainty driven by the human element and the inherent variability of disease progression, treatment responses, and patient adherence. Uncertainty related to clinical outcomes, sample sizes, and statistical power can also impact trial design and efficiency.

It's also important to remember that clinical trials operate within the broader healthcare ecosystem, which is influenced by external factors, such as healthcare policies, market dynamics, patient preferences, and geographical variations. These external factors can affect patient recruitment, impact trial timelines, and influence generalizability of trial results.

The pharma industry must continue to improve its clinical trials. Digital technologies have helped address some of the challenges posed by the pandemic and introduced new trends in the practices of contract research organizations and pharmaceutical/biotech companies when conducting clinical trial analysis. Digital data-capturing technology has ushered in a significant shift, rendering traditional paper-based record-keeping methods obsolete. Advancements in technology also enable more patient-centric approaches to conducting studies, with trials employing data-capturing technologies for remote data collection, reducing reliance on clinical sites. As the industry moves in this direction, it will be crucial for CROs and sponsors to have a comprehensive understanding of virtual, decentralized, and hybrid trial approaches, as well as a solid grasp of real-world data.

Placing patients at the center of clinical trials is crucial, which means involving patients in trial design, ensuring informed consent processes are clear and understandable, minimizing burdensome procedures, and considering patient preferences and perspectives. A more patient-centric approach allows for improved patient recruitment, retention, and supports more credible and valid data.

Embracing digital and virtual technologies can make this possible. However, pharma will need to understand how to handle and analyze the huge increase in data, including real-world data. Trials will need to be carefully designed and processes must be put in place to validate and verify data. Done successfully, the gains are significant: enhanced efficiency, reduced costs, and more accurate data.



A Guiding Light for CRISPR

The story of how Caribou Biosciences developed a hybrid RNA-DNA guide to increase Cas9 specificity – and what the name of the technology has got to do with the Burgundy wine region in France…

CRISPR has captured imaginations and investor interest, with a growing number of companies now developing therapies based on genome editing. We've also just seen the world's first approvals for a CRISPR/Cas9 edited medicine (Casgevy; approved by the UK's MHRA in November and by the US FDA in December 2023). Caribou Biosciences has been working in the area for over a decade and has attracted considerable attention because of its CRISPR chRDNA technology, which can improve the precision of genome edits and reduce off-target events. The company was founded by Rachel Haurwitz (CEO of Caribou) and Jennifer Doudna (joint winner of the 2020 Nobel Prize in Chemistry for her work in gene editing with Emmanuelle Charpentier).

Here, one of Caribou's earliest hires, Paul Donohoue (now Associate Director of Platform Discovery), gives us insight into the early days of the company and how the technology was developed.

How did your experience at the University of California Davis influence the early part of your career?

I grew up in Davis. When I was in high school, one of my science teachers had contacts with a lot of labs at the university and had convinced them to take on undergrad interns. Through this program, I ended up at UC Davis in the lab of Dave Wilson, who was a structural biologist. Dave paired me up with a postdoc student, Eric di Luccio. Eric taught me the fundamentals of science, from how to pipette to molecular biology, cloning, protein expression, protein purification, and some early nuggets around X-ray crystallography and structural biology.

It was really challenging but I was really into the work. It was satisfying to work on super hard problems, such as trying to get E. coli to express a human protein and then purify it to the level that it could be used in solving the protein structure. From these challenges, I learned to appreciate simple things, such as seeing a single clean protein band on an SDS-PAGE gel at the end of a purification process.

I applied to attend college at Davis, and Dave also offered me part-time paid work in the lab. It was basic stuff, such as washing dishes, preparing media, and buffers, but I was also able to continue with protein research with Dave. I ended up working in the lab for the next two years of my undergraduate degree, learning more about protein biochemistry and structural biology. As that wrapped up, another principal investigator, Irwin Segel, who had heard about me from Dave, offered me work in his lab.

Irwin was another formative mentor for me. He had been involved in science for decades and had written one of the earliest books describing enzyme kinetics back when it was a nascent discipline. He was not one to suffer people who weren't driven or scientifically curious. He really imparted a lot of those values on to me, and he also imparted to me an understanding and appreciation of enzyme kinetics, which complemented the structural biology insight and protein chemistry I had learned from Dave's lab.

I was very fortunate to have these opportunities and valuable mentors who were invested in me so early on.

Did you join the pharma industry straight out of university?

No – I went into the wine industry! I was really interested in the applied side of science – and at the age of 21 I was developing a burgeoning interest in wine. I ended up in a science job for the Kendall-Jackson Winery. It was a really informative experience, but it wasn't the type of scientific environment that inspired me. Having that exposure redirected me back to an early research focus and I then went into biofuels, which was fascinating – until the company shut down.

While job hunting, a recruiter reached out about a biotech position researching CRISPR in relation to an opening at

"During the job interview, we spent a lot of time geeking out about x-ray crystallography and protein chemistry."

Caribou Biosciences. I started reading CRISPR papers from Caribou's CEO, Rachel Haurwitz, who had worked in the lab of Jennifer Doudna – Nobel Prize winner in Chemistry in 2020 for her work on CRISPR. Many of Rachel's papers were structural biology based; she was solving the protein structures of Cas proteins, and then coupling this knowledge with fundamental enzyme kinetic characterization of the Cas protein. It reminded me of my work with Dave and Irwin, and I decided this was the environment I wanted to be in.

At the time, Caribou was in an incubator space with just three employees; Rachel, Andy May as the Chief Scientific Officer, and an undergrad intern, who was a computational biologist. Andy was also a structural biologist and, during the job interview, we spent a lot of time geeking out about x-ray crystallography and protein chemistry, and how CRISPR systems worked and could theoretically be applied. There was a lot of energy and excitement – and I was hired for the role. This was back in 2013 and I'm still with the company today.

What is the story behind chRDNA?

In the early days of Caribou, we focused on understanding the basic functional properties of CRISPR-Cas systems and how we could better control their gene editing function. We were particularly interested in understanding the interaction between the Cas9 protein and its guide RNA. Guide RNAs are really interesting molecules because they have lots of secondary structures. We wanted to figure out what elements of the secondary structure were important for driving Cas9- targeting of DNA.

We performed a lot of structural mutations in the guide RNA, including truncating the secondary structures, making them bigger, making sequence changes, and even outright deleting some of the secondary structural elements to see how it impacted the Cas9's ability to target DNA. In time, we understood what parts of the guide were the most important in allowing the Cas9-guide RNA complex to carry out its function.

Something that was interesting to me as I looked at the way the Cas9 protein interacted with the guide RNA was that there wasn't much direct readout of the 2' hydroxyl group on the sugar backbone of the guide RNA backbone by the Cas9 protein side chains. So I started to wonder whether the guide RNA had to be all RNA? Could we go in and replace some of these RNA bases with DNA?

Andy and I decided to try it. We put together some initial designs of hybrid guides that had DNA and RNA, and we ran biochemical cleavage assays against target DNA. I ran the first one with a large collection of these hybrid guides. When I got the data back, I sent a cheeky email and a summary to Andy for him to review – because I thought the results looked great! That night, Andy responded with excited expletives. Suffice to say, he thought it looked great too!

A lot of our initial designs had comparable activity to the normal all-RNA guide. It was a eureka moment. We called these hybrid molecules CRISPR hybrid RNA-DNA – chRDNA for short – pronounced "Chardonnay" (remember I had previously worked in the wine industry!).

As we worked more with these hybrid guides, we also stumbled across some unique properties they had over the all-RNA system. With CRISPR systems, you program the guide RNA to direct Cas9 to a DNA target sequence, but there are some liabilities. The Cas9 protein can bind to and cleave at target DNA sequences that look similar to the intended target site – in other words, off-target sites. Because of this, using CRISPR systems to edit a human cell can pose a risk. You don't always know what off-target sites might be hit and how this will impact cellular function.

To maximize CRISPR genome editing impact, and ensure its safe use, we wanted to find ways to mitigate off-target effects – and this is where chRDNAs began to truly shine. Through a combination of both DNA and RNA bases, chRDNAs have

a very discriminant activity against off-targets. Depending on where we put the DNA bases within chRDNA, we could tune the specificity of the system. In other words, we could build bespoke chRDNAs for each target site.

How is Caribou using the chRDNA technology now?

The complexity of the projects has changed over time, from research of CRISPR tools to development of allogeneic CAR-based cell therapies. For our first clinical program, CB-010, for treatment of B cell non-Hodgkin lymphoma, there are three edits (two gene knockouts and one gene knock-in). In our second program, CB-011, for treatment of multiple myeloma, we make four edits. Our newest program, CB-012, for treatment of acute myeloid leukaemia (AML), involves five edits. As we make more edits, we need a system to help accomplish that with maximum efficiency and safety, such as the chRDNAs.

One of the first patients in our non-Hodgkin lymphoma trial had eight prior lines of treatment before being put on our clinical trial. With a single dose of CB-010, our off-the-shelf CAR-T cell therapy, he has been cancer free for two years. It's incredible to see the impact that these therapies can have for patients. Out of 16 patients we treated in the dose escalation portion of our CB-010 ANTLER phase 1 trial, 44 percent are cancer free out to six months and beyond. It's very humbling to see how our science has directly impacted patients. I joined Caribou because I thought CRISPR proteins were interesting and today it has evolved far from what I imagined.

How has your role at Caribou developed over the years?

Today, I'm an associate director and I lead a small team of highly motivated, very bright researchers. My role is about passing the baton on and relying on my team to come up with new ideas that will drive further innovation in CRISPR systems and how we use them.

In addition to learning to be a manager and a leader, I've had to develop a broader understanding of the biotech space and how a biotech company is run. Sometimes I have to get involved with our business development team and speak to potential partners about our technology, and I've also had opportunities to get involved with our clinical team, talking with clinicians or nurse practitioners about cell therapies. I've also had to interact with our legal team about IP and patents. It has all been very interesting.

Running a team now has also made me reflect on my time at Davis in terms of my early mentors and how I can mentor others. It's important to find the best way to motivate people and to maximize their scientific creativity.

What keeps you excited about the future of CRISPR?

It's been really shocking and surprising to see the rapid implementation of CRISPR across all areas of science. Everything has moved very fast; we're now using CRISPR for cell therapies and for genome editing plants and eukaryotes. It's almost ubiquitous and is already having medical impact with the first approval of a CRISPR-based therapy in the UK coming after just over a decade after the seminal work on CRISPR-Cas9 genome editing by Jennifer Doudna and Emmanuelle Charpentier and their colleagues. It's amazing to take a step back and appreciate how much has changed now that we can make genetic manipulations.

I will never forget when we interviewed a scientist out of his postdoc. He gave a presentation about his work where he had been trying to tag a mouse neuronal protein with a fluorescent reporter. He spent almost a year of his postdoc trying different approaches, but he finished his presentation by saying that the work could have probably been done in two months now that CRISPR-Cas9 was a tool at researchers' disposal. It really encapsulates how much CRISPR has changed things for the scientific community.

And yet it's still early days. There are many new ways that we can push what we're able to do with CRISPR systems and how our understanding and deployment of them evolves.

What are the big challenges facing the field?

One of the biggest challenges for any CRISPR or genome editing company is the speed of advancement. Every week – almost every day – a new paper is released showing how CRISPR is being applied in novel ways. It's a great reminder about innovation and the push to try something new. We scientists often sit down and think about all of the ways that something won't work (and why), as opposed to just getting into the lab and trying it out.

In retrospect when I look back on the early work I was doing on chRDNAs, if I'd have been further in my career and had known more about CRISPR systems, I could have come up with a hundred reasons as to why using DNA and RNA in CRISPR guide sequences would not be tolerated. But we went into the lab and we tried things – and it led to a huge breakthrough for Caribou. And that's something I try to press upon my team. To truly move the needle, you need to come up with a hypothesis, throw some effort behind it, and test it in the lab.

What are your hopes for the future of the field?

I hope that the innovation around CRISPR systems continues and that this isn't where we plateau from a technology perspective. I hope we continue to realize how CRISPR systems can continue to have a broad impact and I hope we continue to find new ways to re-engineer them to push the paradigm of what is possible with cell therapies – and in other areas where there are unmet needs.

I don't see things slowing down any time soon, but whatever lies ahead we must keep in mind the ethical implications. We cannot shy away from the tough conversations in the scientific community; we need to continually ask ourselves that big question:

"Just because we can do something, should we do it?"

Be a Little Different

Sitting Down With…
Luigi Naldini, Director,
San Raffaele Telethon Institute
for Gene Therapy, Milan, Italy

How did it feel to receive the Lifetime Achievement Award at Phacilitate 2024?

It was very rewarding – as with any award! Gene therapy has been neglected for so long, but now there is appreciation from all over the scientific industry. Early on, there were very few of us working and believing in what could be done with gene therapy. Now, there is much better recognition. Although an award goes to a single person, that person doesn't deserve all the credit. This award really goes to a whole team of people who have been involved in different stages.

Have you always wanted to be a scientist?

I always loved science, but early on it was more about nature and wildlife. In high school, I became more familiar with the emerging concept of molecular biology. At that time, there was no real understanding of DNA and RNA, so it was like an entirely new world was opening up – I found that very attractive. I ended up going to medical school, which, at the time in Europe, was a common path if you were interested in a research career in the biomedical area. Although I am an MD, I rarely practice or conduct clinical work. I am more interested in basic science and translational research.

How did you get into gene therapy?

After my MD and PhD, I started work on signal transduction. Back then, we were uncovering the basics of growth factor receptor tyrosine kinase, but I wanted to take a new route. I came across a review about the emerging area of gene therapies by Richard Mulligan (Harvard). After the early hype of gene therapies and the lack of results, he explained that we needed to go back to the hard science.

I was attracted by this idea and I wanted to join the field. I went to the US and I applied to Richard Mulligan's lab, but I didn't get the role! Over the years, I became very close to him and he always said, "Too bad you couldn't come to my lab."

And I would reply, "I could have come to your lab, but my application was rejected!" Fortunately, I was also interviewed at the Salk Institute and ended up in the lab of Inder Verma.

Why focus on lentiviral vectors?

At the time, there was discussion around current vectors, such as the gamma retroviral vector, not being very efficient. On the floor above me was the lab of Didier Trono working on HIV. It was early days for HIV and there was a lot of work focused on understanding this deadly retrovirus, which was very efficient at infecting human cells. We thought, why not try creating a vector from HIV? I was interested in starting something from scratch in gene therapy rather than joining something that was already going on, so building a new vector was very appealing. Though we never dreamed it would become so useful!

I worked for two years on this project – and it was very difficult at the beginning, particularly as it was a new area for me. I spent at least a month in the library, browsing literature (which is amazing to think about today, given that you can do that in a matter of days using the internet!).

We tested the lentiviral vector we had developed in the brain of a mouse. Could we prove transfection of a neuron? The "eureka" moment was when we got that neuron shining with GFP. It was a big accomplishment – and after that I planned to return to Europe. However, a biopharma company was interested in licensing the technology for product development.

I resigned from my position in Europe and began working with the company to develop the vector for clinical trials in humans. However, the whole field came to a halt because there were reports of tumors developing in patients treated with a gamma retrovirus in Europe. Theoretically, we should have anticipated this but there was not high recognition of the risk at that time. Many companies were scared away from gene therapy – including the company I was working with.

At this point, I returned to academia in Italy and I continued to develop the technology on an academic basis – thanks to funding from the Telethon Foundation and other sources. We also collaborated with researchers in France and eventually we took our lentiviral vector into clinical testing and showed that it was safe.

Paradoxically, an HIV-derived vector was safer than the earlier gamma retroviral vectors! We really did work hard to disable the original virus and improve the safety – but the results went beyond expectation. If treated early enough, children can now be cured of very deadly diseases. Our work attracted people back to gene therapy – including big pharma. Together with the Telethon Foundation CEO we spoke with GSK executives and this led to an alliance for the development of hematopoietic stem cell gene therapy. We developed a handful of successful treatments with them, including the first ex vivo stem cell gene therapy approved worldwide.

All of this work took more than two decades.

How did it feel when lentiviral vector therapies made it to market?

Progress doesn't happen in a single moment. Yes, early experiments can have a "eureka" moment but it takes time to bring this to humans. When you see results in patients and the disease doesn't seem to be appearing, you need to wait months before you can be sure of the results. It also then takes time to get to market. But it feels amazing!

The whole experience has been a learning curve for us as well as the industry. I feel very lucky that I've been so closely involved, from the early steps on the bench, to clinical, and then to market. I've also been able to see the challenges from both academic and industry levels.

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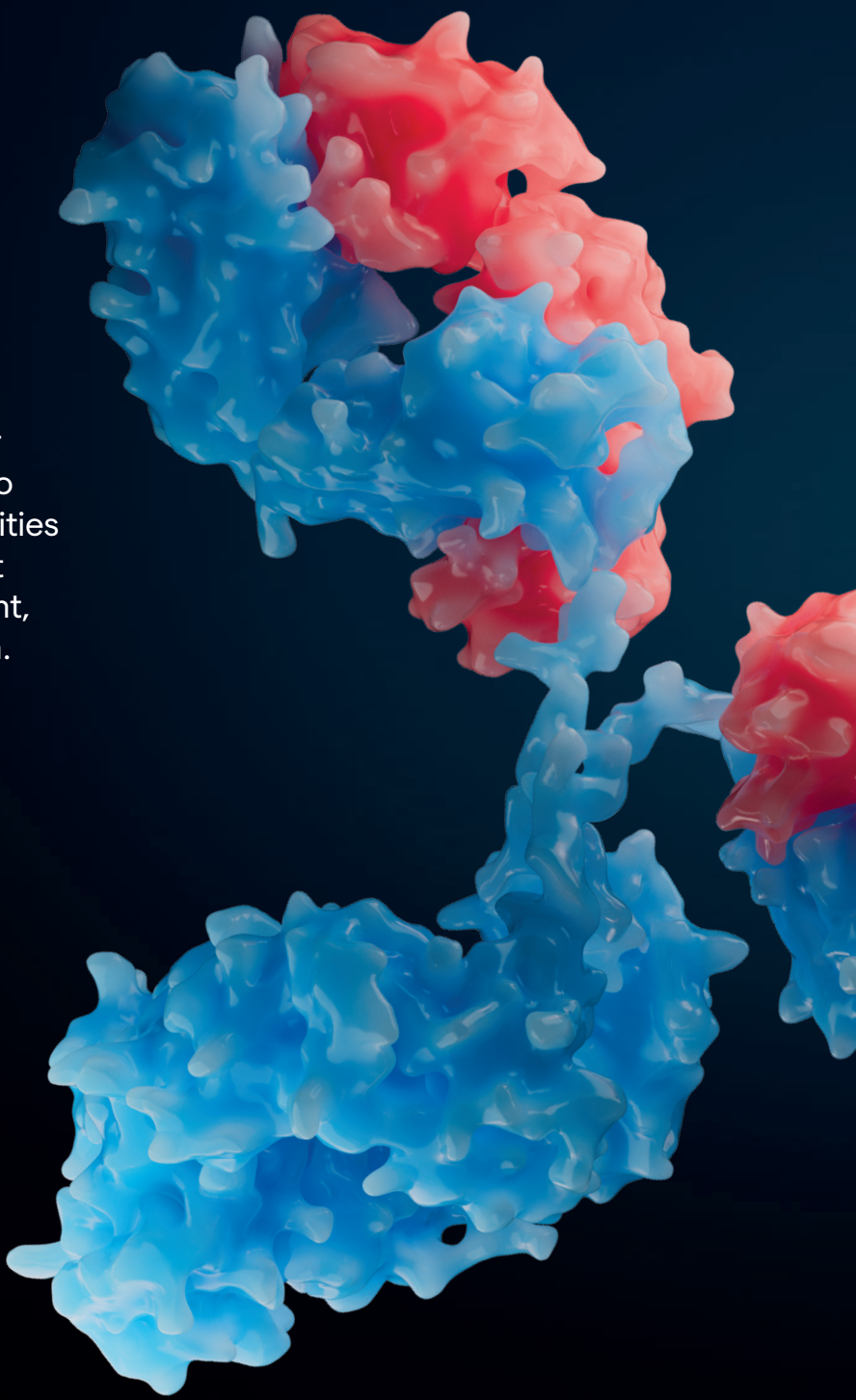

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