pharmaphorum deepdive

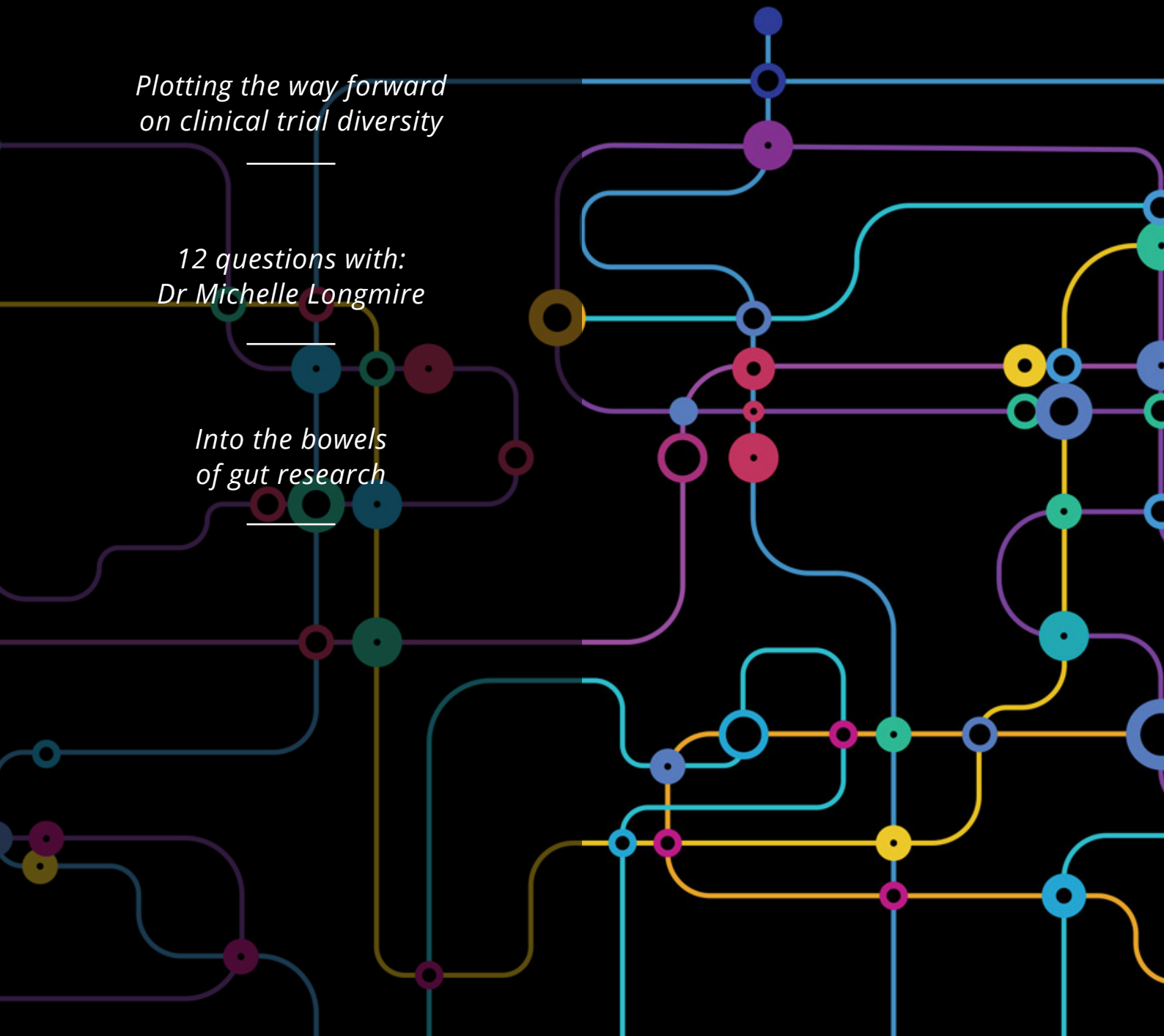
Inside the organ chip revolution

February 2023: R&D

Plotting the way forward on clinical trial diversity

12 questions with: Dr Michelle Longmire

Into the bowels of gut research



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Deep Dive: Research & Development 2023

Welcome to a new year for pharmaphorum's Deep Dive! While we may only be two months into 2023, amid growing pressure to justify high drug prices, address trial backlogs, and manage staffing shortages – while continuing to develop lifesaving treatments for patients around the world, life sciences companies have certainly started the year off with a bang.

Not that drugmakers have been deterred. In fact, with news that the US may be on the cusp of approving the world's first CRISPR gene therapy, there are clear signs that innovation in R&D remains a guiding light for companies as they navigate an uncharted and uncertain industry landscape.

Inspired by the dedication shown by researchers working to drive developments in the lab, here at Deep Dive we too are looking to kick off 2023 with a renewed determination to bring you the biggest and most influential stories from across the life sciences. So, it seems only fitting that we begin with an issue dedicated to the innovators and ideas set to disrupt the status-quo over the coming months.

In this edition, find out how organ-on-a-chip technology is changing the way that drugs can be evaluated, learn about efforts to champion diversity in clinical trials, and get an inside look at key R&D trends straight from the mouths of industry leaders.

We are also thrilled to bring you a new format for the magazine. In our '12 questions with' features, we will get to know the people behind life sciences headlines in order to find out more about those leading the charge for the future of healthcare.

For all this and more, read on.

Eloise

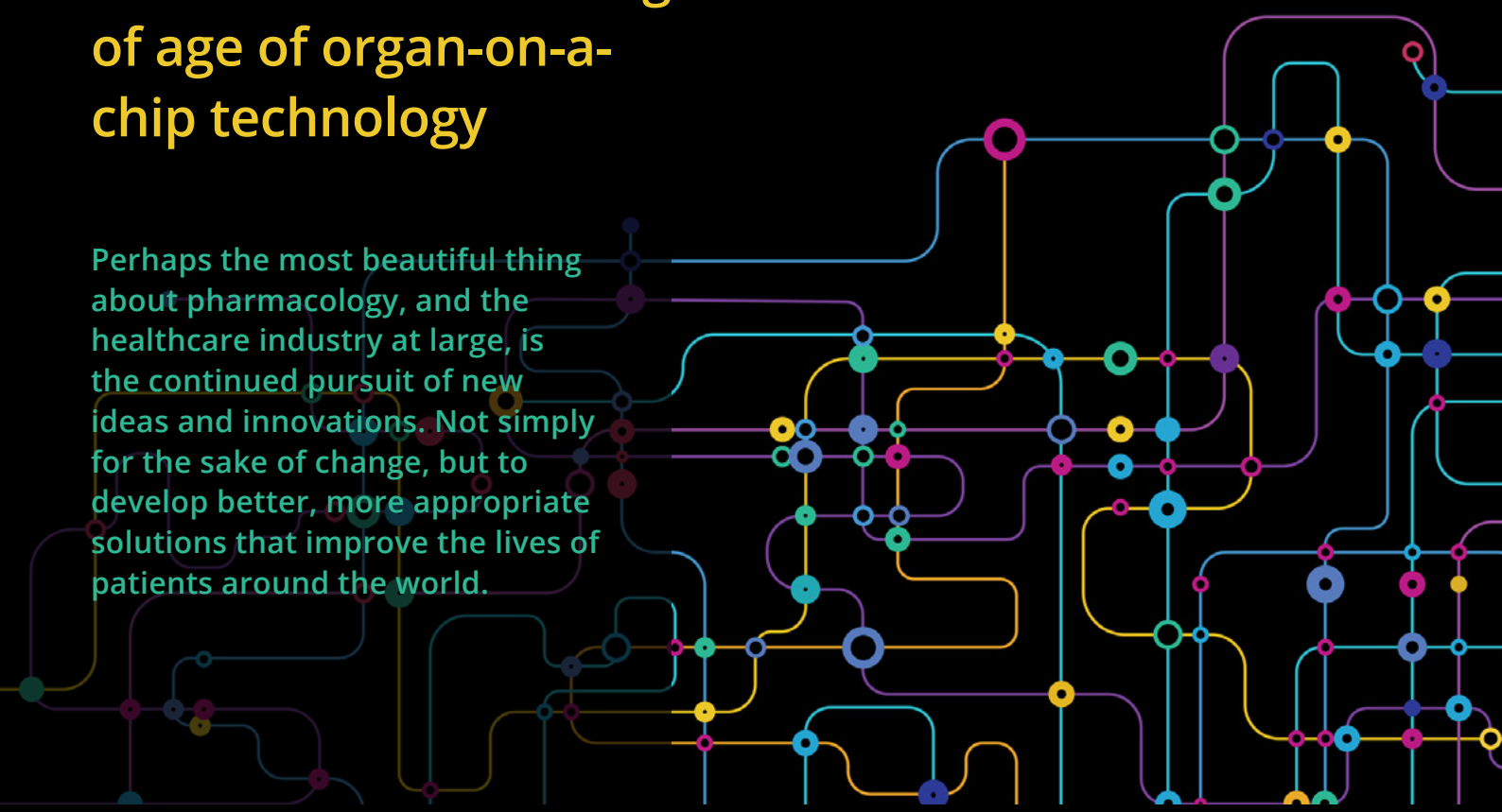
Eloise McLennan – editor, Deep Dive

Next issue:
Market Access (April 2023)
Plus:
• Bringing DTx to patients
• A history of HIV treatments

Catch up on recent issues:
Digital Health – November 2022

Patients & Partnerships – October 2022

Inside out – the coming of age of organ-on-a-chip technology



Perhaps the most beautiful thing about pharmacology, and the healthcare industry at large, is the continued pursuit of new ideas and innovations. Not simply for the sake of change, but to develop better, more appropriate solutions that improve the lives of patients around the world.

However, drug development is notoriously slow and expensive. On average, it can take up to ten years for a drug to make it from lab to market, if it even makes it through approvals at all, given that approximately 90% of drugs fail to make it to market.

By law, human and animal testing is required before a drug can be approved. However, this approach has limitations. Take mouse models, for example. In theory, given that mice and humans share 92% of their DNA, drug candidates that successfully target and activate genes in mouse models should achieve the same results in humans. And yet, many drugs fail to make this leap from mouse to human.

Oh, to be a mouse would be a fine thing indeed. The trouble is, that we are not, and so conditions such as Alzheimer's disease, cancer, and diabetes – ailments that have all been cured in mice – continue to impact patients worldwide.

While animal models have, in the past, played a vital role in developing lifesaving drugs, in an industry where good enough is never really good enough the limitations of this approach naturally became the target for innovative thinkers. In a bid to replace, refine, and reduce reliance on animal models, high-tech alternatives began to emerge, allowing drugmakers to explore new ways to unlock the molecular mechanisms causing modern diseases.

And so began the era of organ-on-a-chip technologies. But how did we get from 2D cell cultures to a series of increasingly complex and connected miniature tissues designed to better mimic human physiology through controlled cell microenvironments and tissue-specific functions?

Let's find out.

1907

The era of 2D culture

As with many a tale in drug development, the origins of organ-on-a-chip technology begin in the early 1900s, when American biologist and anatomist, Ross Granville Harrison published the results of his successfully cultured frog neuroblasts in a lymph medium. Through his findings, Harrison demonstrated that nerve fibres develop without a pre-existing bridge or chain and that tissues can be grown outside of the body.

During the 1950s, researchers would build on this concept with the development of 2D cell cultures. This method involved growing cells on a flat surface, usually a petri dish, covered in a nourishing material called a growth medium, which allowed cells to form a monolayer that researchers could easily observe and manipulate. Before this, cells were grown in suspension in test tubes, which limited researchers' ability to study cell behaviour and interactions.

Although the exact inventor of 2D cell cultures is unknown, key pioneers in the field include George Gey, who developed the first permanent cell line, and Jonas Salk, who established the first cell culture laboratory. These and other scientists laid the foundation for the widespread use of 2D cell cultures in cell biology research.

1960s

The origins of microfluidics

While it would be another 50 years until organ-on-a-chip technology emerged, the story of this ground-breaking innovation could not be told if it were not for the discovery of microfluidics.

The history of the field can be traced back to the late 1960s, when researchers first began to develop systems for handling small fluidic volumes, typically in the microlitre or nanolitre range.

Over the following two decades, advances in microfabrication technology and materials science led to the development of increasingly sophisticated microfluidic devices, such as lab-on-a-chip systems.

Credit: University of Washington Photo

The development of microfluidic technology has been a key enabling factor for organ-on-a-chip technology. Microfluidic devices are used to control the flow of fluids and nutrients in the device, creating a controlled environment that mimics the human body. These devices are typically made from materials such as silicone or plastic and are designed to recreate the physical, chemical, and biological conditions that exist in human organs and tissues. This allows researchers to test drugs and other compounds in a more human-relevant context, providing better predictions of human response and reducing the risk of late-stage clinical failures.

1980-1999

Cultures enter a new dimension

Recognising the limitations of 2D cell cultures, researchers began to search for a way to represent the complex in vivo microenvironment more accurately. The result: 3D cell cultures. The exact date of the invention of 3D cell cultures is difficult to determine, as it is the result of the collective effort of multiple researchers and scientists over a period of several decades. However, the first use of "three-dimensional culture models" is commonly attributed to early studies published in 1989 and 1992.

3D cell cultures aim to better replicate the in vivo conditions by creating a three-dimensional structure for cells to grow in, which more closely resembles the native tissue architecture. This allows for more accurate modelling of cell-cell interactions, signalling, and functions. Key pioneers in the field include András Nagy, who was one of the first to report the successful generation of 3D structures using mouse embryonic stem cells, and Maeve Duffy, who developed a technique to generate 3D structures using hydrogels.

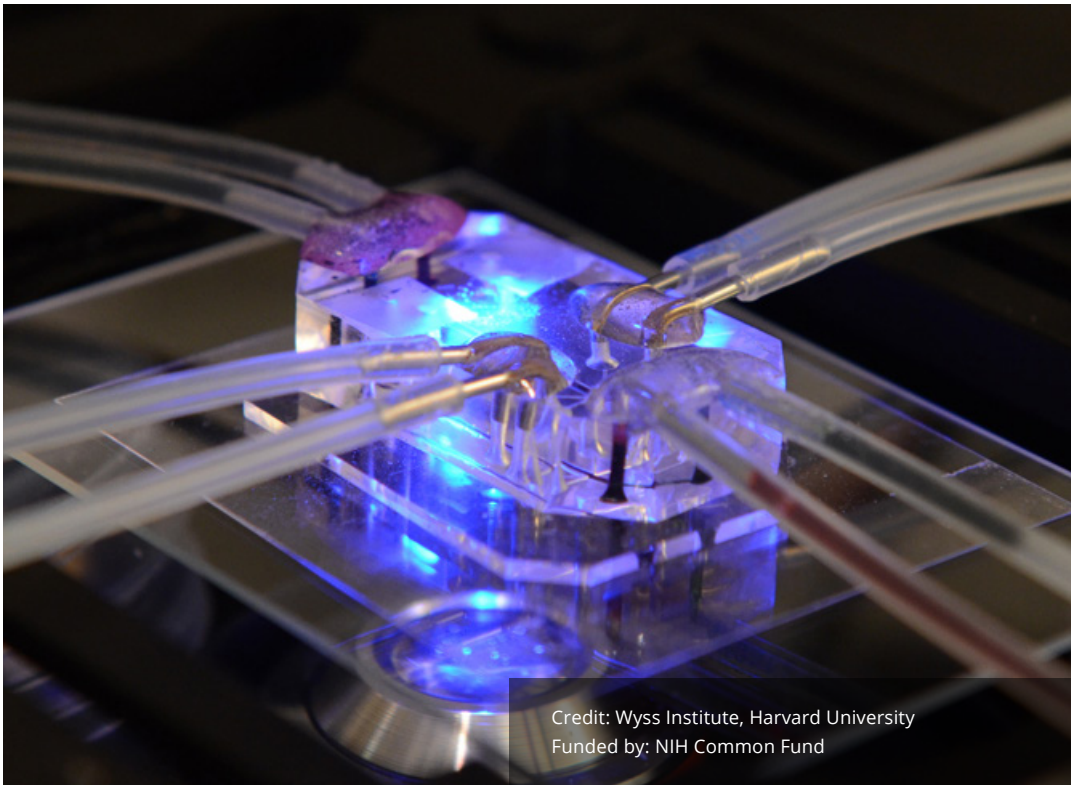
These cell cultures can be generated using a variety of methods, including scaffold-based systems, hydrogels, and organoids. The increased complexity and more physiologically relevant conditions offered by 3D cell cultures have broadened their use in various fields, including drug discovery, disease modelling, and tissue engineering.

The first successful organ-on-a-chip developed

The first organ-on-a-chip was created by researchers at the Wyss Institute for Biologically Inspired Engineering at Harvard University in 2010. Led by Donald Ingber, the team developed a "biomimetic microsystem", capable of reproducing complex integrated organ-level responses to bacteria and inflammatory cytokines in the lung alveolar.

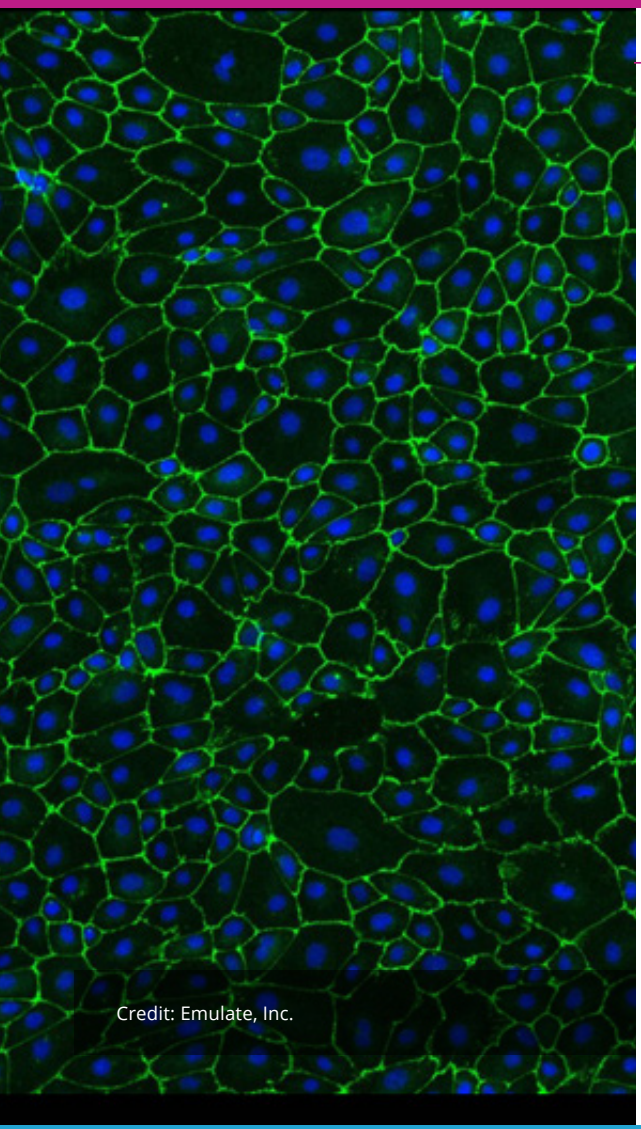
The microfluidic device established a new approach to tissue engineering, as it incorporated two layers of living human-cultured tissues – epithelial cells and endothelial cells – onto a porous, flexible material, approximately the size of an eraser. To mimic the natural responses of living lungs, air is delivered to the lung lining cells, while a rich culture medium flows in the capillary channel to replicate blood flow and cyclic mechanical stretching imitates the breathing process. Together, these unique features enabled researchers to study drug toxicity and disease progression in a way that closely resembled the human body.

To test just how closely this pioneering technology performed as a dupe for the human lung, researchers introduced living E. coli bacteria into the air channel, while simultaneously allowing white blood cells into the capillary channel. Results from the study showed that the lung cells were able to detect and respond to the bacteria's presence, triggering an immune response that mobilised the white blood cells to destroy the E. coli in the air chamber.



Credit: Wyss Institute, Harvard University
Funded by: NIH Common Fund

2013



Credit: Emulate, Inc.

New materials create new opportunities

As the potential of organ-on-a-chip technologies gained greater attention from researchers within the pharmaceutical industry, advancements in the quality and quantity of materials for their fabrication were inevitable.

While polydimethylsiloxane (PDMS) was – and still remains – the predominant material used for organ-on-a-chip devices, due to its ease-of-use, biocompatibility, and relatively low microfabrication costs, it does have limitations. PDMS is hydrophobic in nature, which restricts the attachment and the spreading of cells.

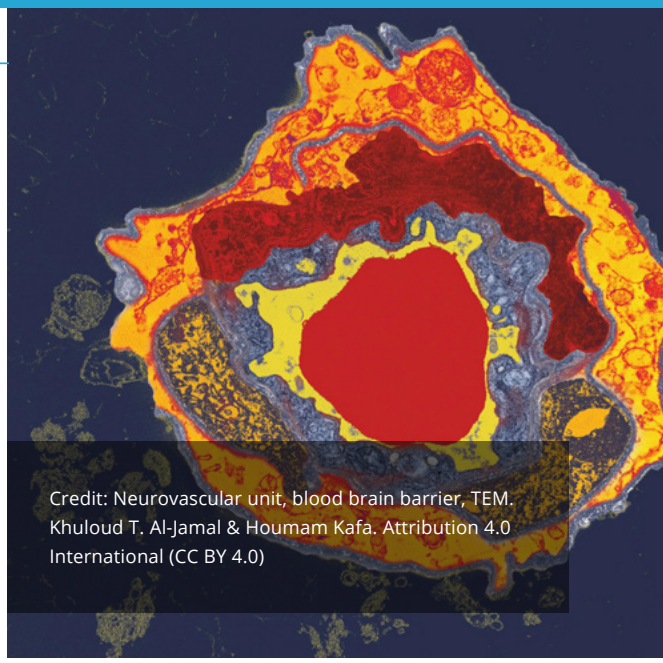
And researchers began to explore alternatives, including Annabi et al, published in 2013. In the study, the team developed a new technique to address the challenges of PDMS-based devices, by coating microfluidic channels with hydrogels - specifically methacrylated tropoelastin (MeTro) and methacrylated gelatin (GelMA) – which provided a suitable environment for cardiomyocyte (CM) attachment inside of the channel. This development, alongside other advancements, opened doors for research to pursue on-chip cardiac cell cultures.

2016

Breaking barriers in biology

The blood-brain barrier is notoriously good at preventing unwanted substances from accessing the brain. More often than not, this is a highly necessary function. However, it does pose a significant impediment for pharma companies, as many potential drug treatments struggle to breach it.

As part of efforts to drive research in the sector, in 2016 researchers at the Wyss Institute developed a blood-brain barrier-on-a-chip, mimicking the barrier that separates the brain from the bloodstream. To form the chip, the team fabricated a long, narrow lumen inside of a clear polymer chip, designed to reflect the shape of a blood vessel, which was filled with a collagen matrix containing human brain



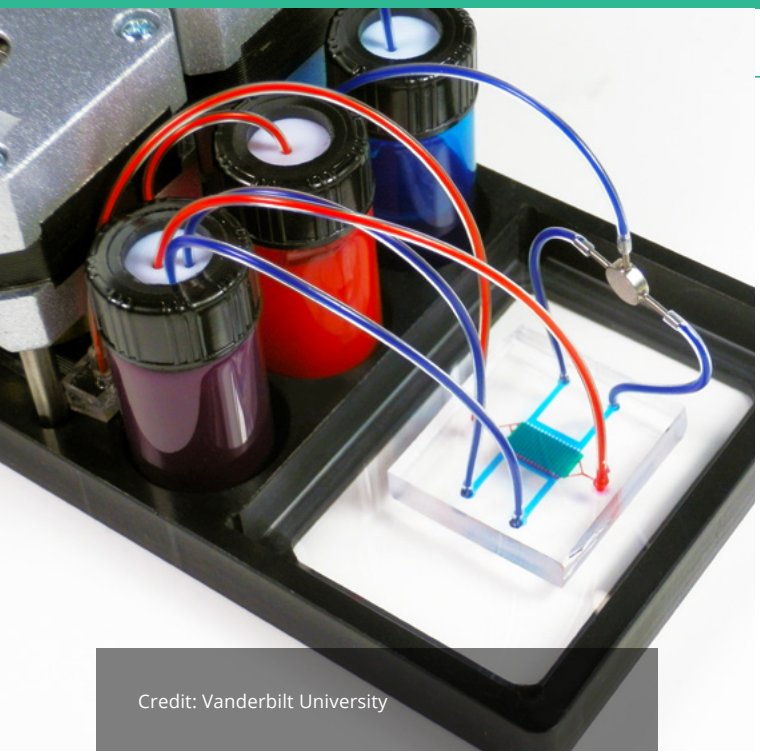
Credit: Neurovascular unit, blood brain barrier, TEM. Khuloud T. Al-Jamal & Houmam Kafa. Attribution 4.0 International (CC BY 4.0)

astrocyte cells and lined with living human endothelial cells. Human brain pericyte cells were subsequently placed inside the lumen to complete the chip.

Using the blood-brain barrier on-a-chip model enabled the research team at Wyss to study neuroinflammatory response in vitro by introducing a pro-inflammatory protein commonly associated with diseases of the central nervous system, including Alzheimer's, brain ischemia, multiple sclerosis, stroke, and traumatic brain injury.

That same year, in a slightly unusual turn of events for organ-on-a-chip research, the National Institutes of Health (NIH) teamed up with NASA and the International Space Station (ISS) to launch the Tissue Chips in Space programme. The goal? To better understand the role of microgravity on human health and diseases and translate those findings to improve human health on Earth. The first of these NIH-supported chips was – quite literally – launched in December 2018. This immune-system chip was closely followed by the launch of four additional tissue chip projects: lung and bone marrow, bone and cartilage, the kidney, and the blood-brain barrier.

2017



Credit: Vanderbilt University

US FDA sets its sights on Organs-on-Chips technology

Recognising the rapid advancement of microfluidic devices and the multiple different organs now replicated in chip form, in April 2017 the US Food and Drug Administration (FDA) announced plans to enter into a multi-year cooperative research and development agreement (CRADA) with Emulate. First unveiled in 2014, Emulate – a spin-out from Harvard University's Wyss Institute – had already amassed a comprehensive portfolio of organ-on-a-chip products.

Under the deal, Emulate and the FDA set out to evaluate and qualify the use of Emulate's Organs-on-Chips technology as a platform for toxicology testing in order to meet regulatory evaluation criteria for products – including foods, dietary supplements, and cosmetics.

2018

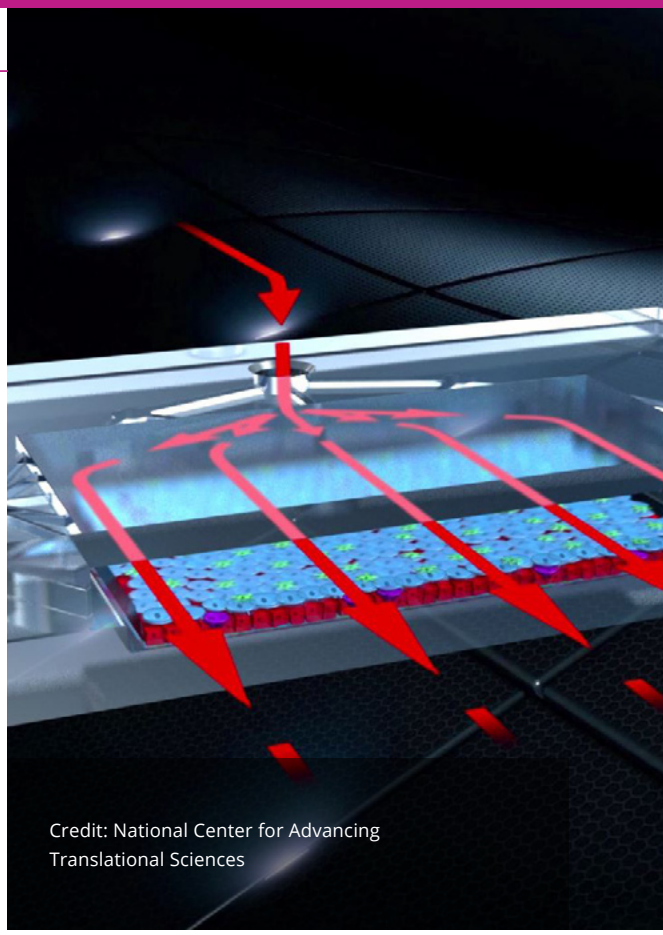
Organ-on-a chip takes the main stage of pharma

Having racked up multiple success stories of organ-on-a-chip technologies demonstrated by research teams around the world, it wasn't long before big-name industry players began to pay attention to this burgeoning sector.

As such, 2018 was a big year for partnerships between organ-on-a-chip start-ups and Big Pharma companies.

In February, Roche and Takeda announced plans to partner with Emulate. Through the three-year partnership, the pharma giants gained access to Emulate's array of organ-chips for testing the efficacy and safety of new antibody therapeutics and combination therapies.

Later that year, AstraZeneca also signed on to partner with Emulate and incorporate organ-on-a-chip technology into the pharma giant's R&D programme. This built on previous work between the two companies, which began back in 2013.



Credit: National Center for Advancing Translational Sciences

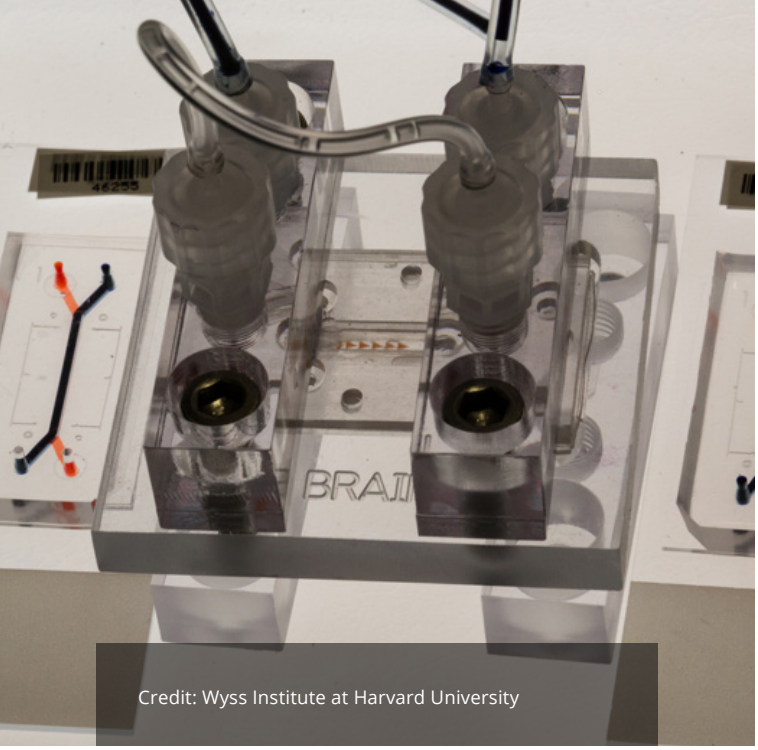
2022

Enter the OCTOPUS

If you hadn't already guessed, this is not an actual octopus. The Organoid Culture-based Three-dimensional Organogenesis Platform with Unrestricted Supply of soluble signals (OCTOPUS) is, in fact, an organoid device developed by a research team at the University of Pennsylvania School of Engineering and Applied Science.

Lead by Dan Huh, a notable figure in the early development of organ-on-a-chip devices at Wyss Institute, OCTOPUS is designed to bring us closer to finally achieving the goal of a "human-on-a-chip".

Although immature organoids can generate a wealth of valuable information for researchers, when it comes to replicating the true complexity of living human organs, maturity is key. As such, finding ways to nurture organs-in-a-dish to greater levels of maturity has been a notable area of research. This is where the team behind OCTOPUS claims to have significantly advanced the frontiers of organoid research.



Credit: Wyss Institute at Harvard University

OCTOPUS, they claim, reimagines the 3D geometry of the hydrogel culture material, splitting this scaffold into a tentacled configuration to better mimic the complex and dynamic environment of the human body. These thin culture chambers sit on top of a circular dish, approximately the size of a US quarter coin. With this format, Huh and his team demonstrated accelerated production of intestinal organoids with significantly enhanced structural and functional maturity, as well as continuous development over a four-week period.

2023

A new era for research enters US law

Heading into a new year, the US Government marked a clear turning of the tide for clinical R&D with the introduction of the FDA Modernization Act 2.0. Signed by President Biden at the very tail end of December 2022, the Act repealed a long-standing requirement that experimental treatments be studied in animal models before they can be considered for human trials.

Instead, the legislation authorises the use of alternative methods – such as organ-on-a-chip – alongside animal studies, to investigate the safety and effectiveness of a drug.

While this Act is unlikely to transform the R&D landscape overnight, it is a clear sign that regulators, industry experts, and researchers are confident that organ-on-a-chip technologies, organoids, and computer models, have an important role to play in advancing the future of medicine.

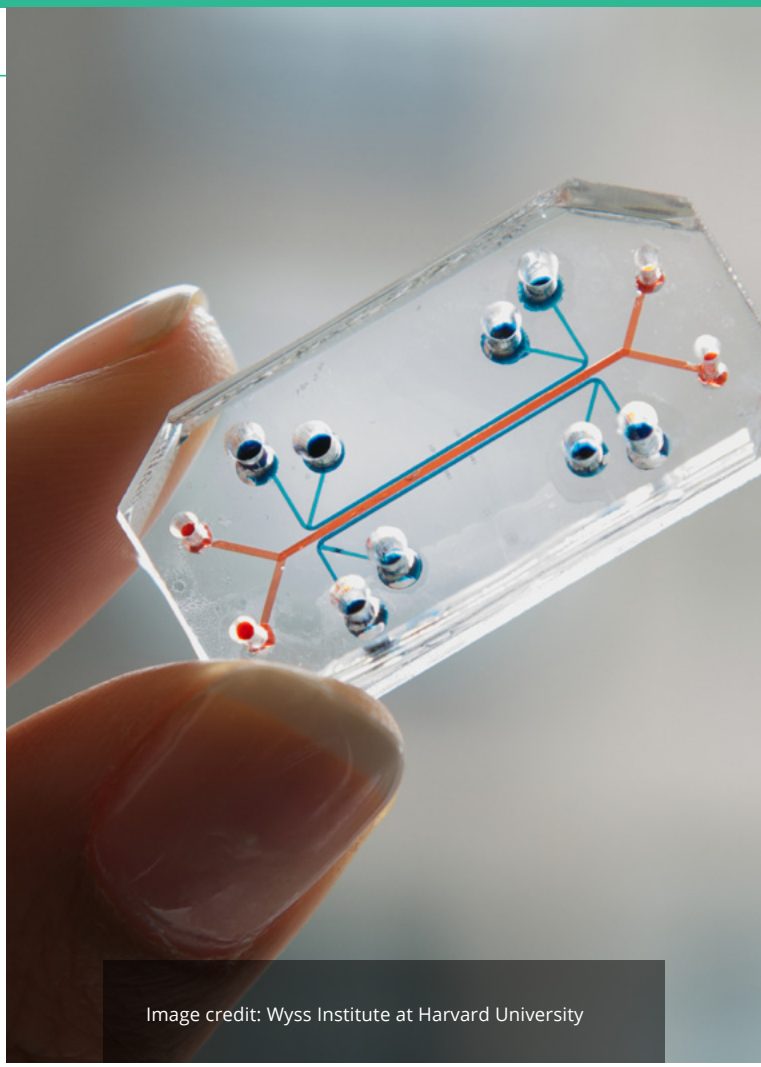
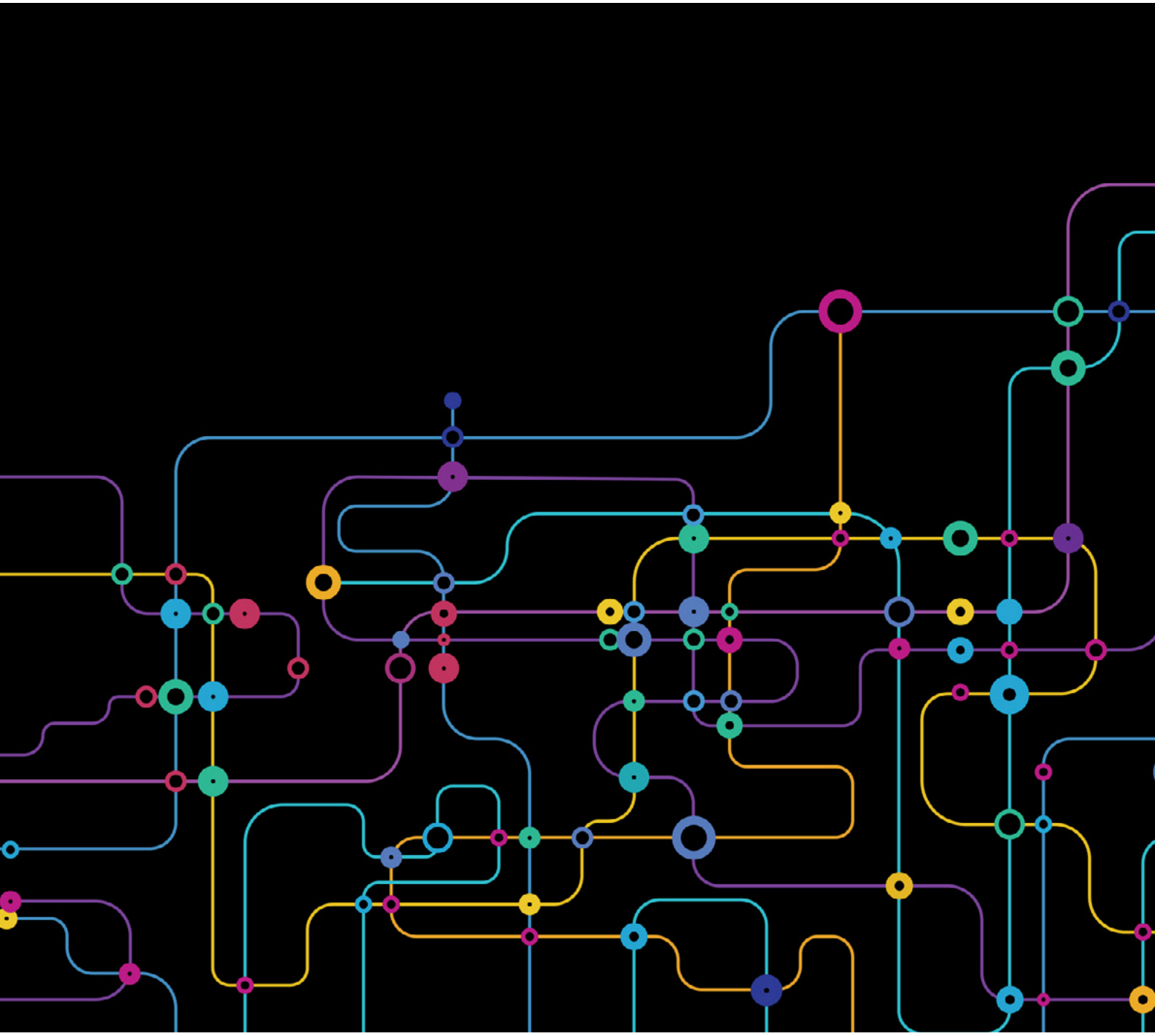


Image credit: Wyss Institute at Harvard University

About the author

Eloise McLennan is the editor for pharmaphorum's Deep Dive magazine. She has been a journalist and editor in the healthcare field for more than five years and has worked at several leading publications in the UK.



12 questions with:
Dr Michelle Longmire

As the co-founder and chief executive officer of Medable, Dr Michelle Longmire is mission-driven to accelerate the development of new therapies for disease. A Stanford-trained physician-scientist, Dr Longmire witnessed first-hand the critical barriers to drug development – including the time and costs associated with clinical trial participation. She founded Medable to pioneer a new category of clinical trial technologies that remove traditional roadblocks to participation and radically accelerate the research process.

1 What was your background prior to this role, and how did it prepare you for the work you do now?

I learned a lot of the key qualities of being a CEO from team sports and my experience conducting research at Stanford. It was the perfect combination that directly applies to leading the team at Medable, with a strong focus on our mission to get effective therapies to patients faster, plus the relentless drive and working as a team to reach our goals.

I truly believe all extraordinary work is achieved by empowering your team. As a CEO, I think the most valuable thing I can do to empower my team is to provide a clear vision of what's possible and where our goal is to evolve drug development to improve human health and lives.

The mission was born while I was conducting research on systemic sclerosis at Stanford. I was looking at identical twins with this disease to try and understand differences in identical twin pairs – why one would have the disease and the other one wouldn't, or why one would not have as severe clinical manifestation. Facing the hurdle of trying to enrol patients who had the unique requirements of being identical twins with this rare disease, I realised there has to be a better way to overcome the limitations of getting participants to Stanford to participate.

Team sports taught me that the team is always stronger than the individual parts. When everybody is dedicated to achieving a singular outcome, we can do things that are seemingly impossible. Being a CEO is the most difficult job I've had. However, through my experience running Medable, I have learned that being relentless through setbacks, turbulence, and anything else we might encounter is the key to achieving our mission and shaping the industry into a better future.

2 What are some of the biggest ongoing challenges in your work?

The last three years have been incredibly challenging and exciting. The biggest challenge is really around scaling the company to meet the incredible demand we experienced. The surge in demand for DCT during the pandemic was exhilarating and really proved the idea that technology can be a game changer when it matters most. The adoption curve was accelerated radically, and we needed to dramatically scale our workforce and company in a very short time frame.

Demand has not diminished, and this requires us to focus on delivering a best-in-class consumer-grade experience for patients, sponsors, and investigators on a worldwide scale. We are excited about how far we have come and inspired by the impact we are poised to make to improve human health.

3 What motivates you about working in pharma?

There are thousands of diseases that we do not have treatments for, or we have suboptimal treatments for, and even for conditions where there are treatments, there are still barriers and challenges to access. As a practising physician, I see these challenges first-hand. I believe that if we can radically accelerate the speed of clinical development, we can have treatments for all human conditions within our lifetimes.

Working with pharma is exciting because we have the benefit of reach, scale, and meaningful partnerships working together to truly innovate the drug development process. Getting those effective therapies to patients faster is incredibly motivating to me.

4 What are your biggest long-term goals for five years or ten years from now?

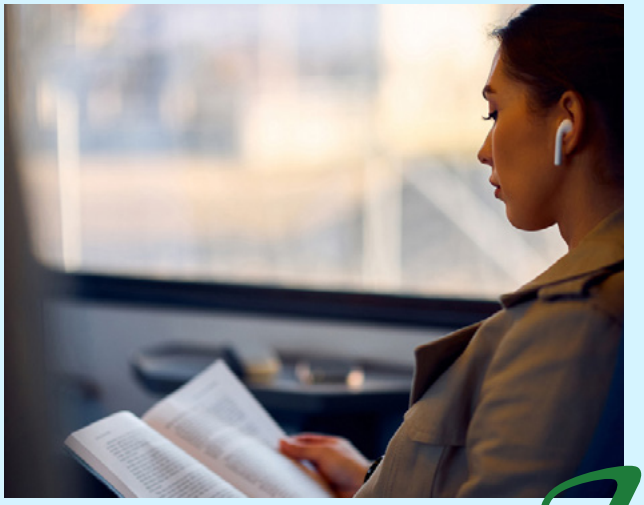
Our goal is to radically reduce clinical trial timelines from many years to under a year. In order to do that, we need to transform clinical development with technology at a global scale that gets increasingly better with time.

At our current pace of drug development, it will take 200 years to find cures for all disease; we want to improve that tenfold. So instead of taking 200 years to discover cures for these diseases, we reach that in 20 years. We think we can get there in ten years.

5 What are the most important professional skills in your work, and how do you hone them?

As a CEO, I know it's important to continue learning and growing. What gets the company to one level of growth usually does not get it to the next. So, I try to look around the corner and think about what I need to learn and how I need to grow to prepare for the next phase of the company's growth. I am constantly reading, working with my coach, seeking out new ways of doing things, and thinking about how to improve.

6 What do you see as the biggest challenges facing the industry right now?



In clinical development, the use of digital technologies is being increasingly encouraged, as evidenced by the recent regulatory guidance in both the US and Europe. The biggest challenge now is adopting DCT technology at a full enterprise scale. We've proven that DCT works and adds incredible value to clinical trials. Now our next challenge is scaling these results quickly.

7 How do you promote patient-centricity in your workplace?

Medable is really focused on improving patients' lives, and to do that, we need to understand their lives. We have a Patient Caregiver Network that works directly with participants and product teams to provide valuable feedback to enhance usability.

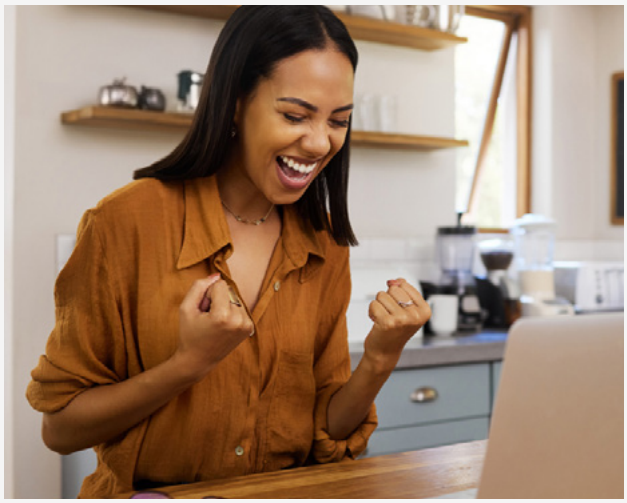
We also bring the patient experience to our entire team, inviting a speaker to a monthly all-hands meeting to tell their story. That patient voice is so valuable to us because improving patient lives is really at the heart of everything we do.

8 How has digital technology changed your work or workplace culture?

Medable is a remote-first company, even before the pandemic. We believe in the power of digital tools to bring people together even though they are in different geographies and from different cultures. This is only possible because of technology – it expands the horizon of what is possible.

9 What advice would you give to a young person starting out in your field?

I would say choose something you can be completely obsessed with. The stakes are very high in healthcare and life sciences, given you are directly impacting individual lives, so, getting things right is an extremely important and never-ending pursuit. But if you're passionate about your "why" and driven to see results, that will carry you through the inevitable challenges we all face in work.



10 What are your hobbies? What do you do in your free time?

I believe in the stoic concept of a sound mind in a sound body. In my free time, I exercise and learn (sometimes at the same time!). I'm often on the road, so I either go for a run or attend an exercise class – one of my favourites is Barry's Bootcamp.

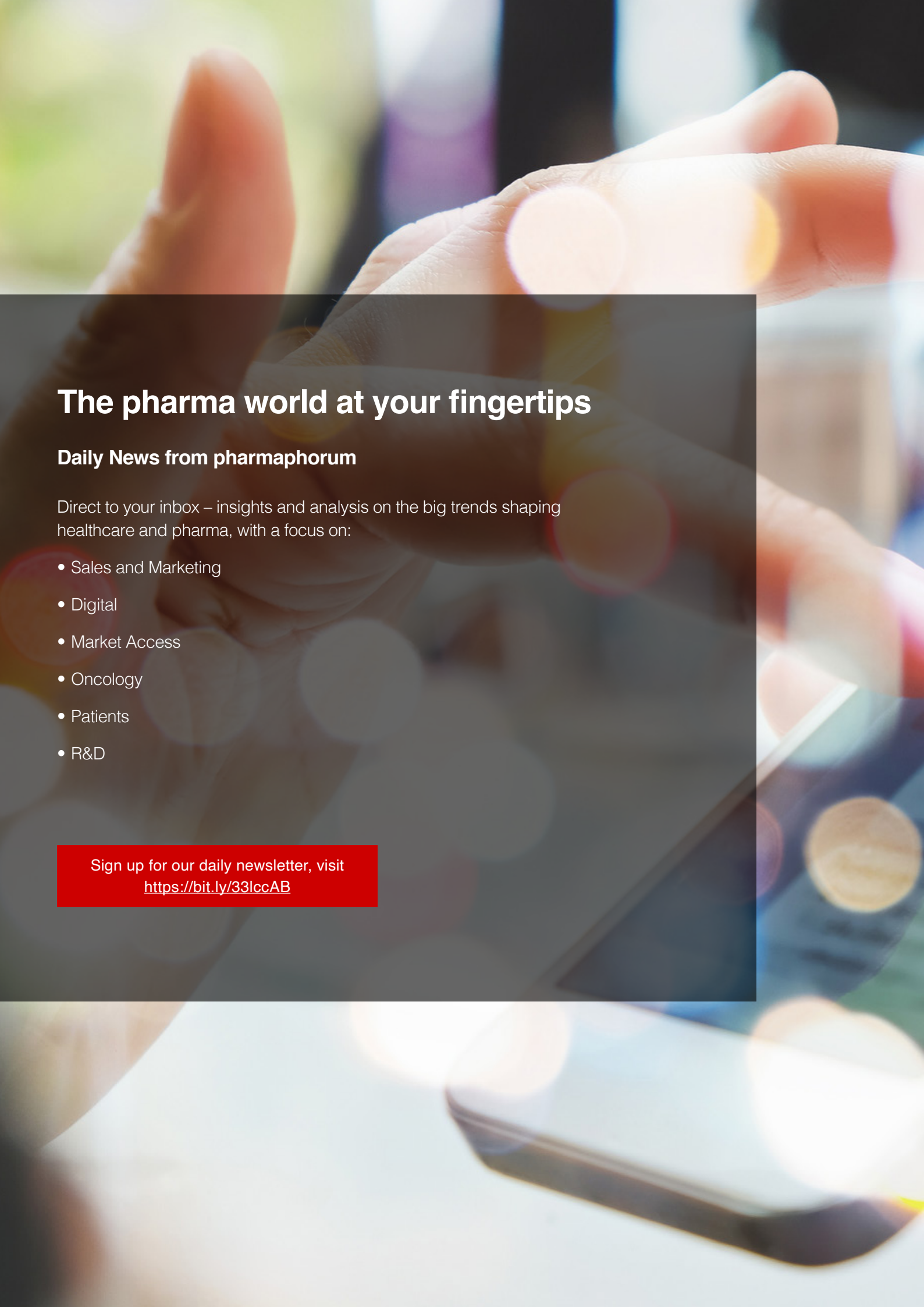
When I'm at home in Colorado, I downhill and Nordic ski in the winter and run, bike, and rollerblade in the summer. The audiobooks and print books I read are typically either scientific topics like quantum physics, mathematics, biology, or medicine and business books written by or about CEOs and leaders I admire.

11 Do you have any pets? What are their names, and what are they like?

Yes! I have two very energetic and active French bulldogs, Bella and Nadia. Nadia was named after the gymnast Nadia Comăneci because she is incredible at climbing on tables and furniture.

12 How do you manage health, fitness, and wellness in your life?

I know that if I don't get the exercise I need and take care of myself, I'm not going to be able to show up as the leader my team needs so that we can accomplish our mission. Therefore, I'm very deliberate about making sure I limit how many calls I have per day so that I have enough time to exercise and rest. Exercise is the best stress management tool ever "invented".



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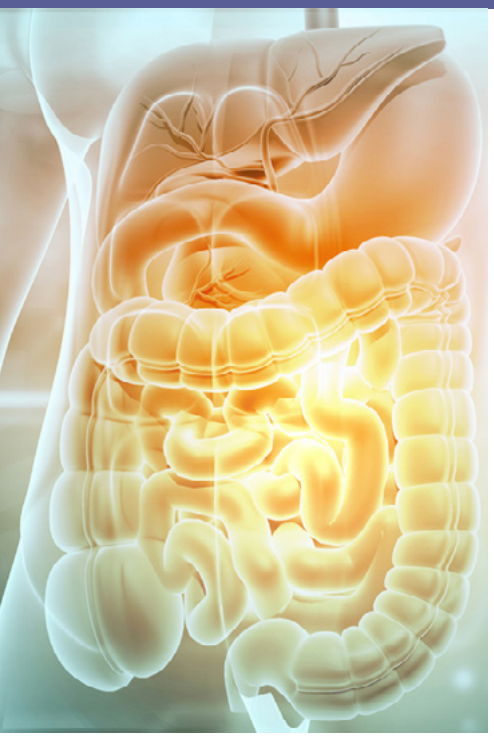
Into the bowels of gut research

For people living with Inflammatory Bowel Disease (IBD), navigating life around the risk of flare-ups can be a messy and exhausting challenge. According to the EFCCA, there are ten million people worldwide living with IBD, an umbrella term used to describe disorders that cause chronic inflammation of your gastrointestinal (GI) tract.

There are two primary forms of IBD – ulcerative colitis and Crohn's disease – both of which have a marked impact on a person's daily life. As with the majority of health conditions, symptoms and severity vary from patient to patient; however, common experiences include persistent diarrhoea, abdominal pain, weight loss, and fatigue.

IBD conditions are often episodic in nature. Symptoms can go into remission for days, months, or even years before a flare-up occurs. For researchers, this complicates matters, as monitoring and treating a fluctuating condition over time requires a great deal of information about both the nature of IBD, and the external environmental factors that exacerbate symptoms.



While there is still no cure for IBD, multiple treatments have been approved to help patients achieve and maintain remission. This gives the lining of the gastrointestinal tract a chance to heal, something that can substantially improve quality of life for the patient. The challenge is, when patients exit the clinical setting, the appearance and severity of their symptoms don't stay static. One bite of the wrong food at the wrong moment can throw a spanner in the works.

This is a big problem for treatment, as practitioners can only make therapeutic decisions based on the information they are given. As such, it is vital that organisations fill the gaps in IBD knowledge to accelerate IBD research and drug development. Verily, Alphabet's life sciences research arm, is one such company working to develop a more holistic understanding of IBD, with help from those who know their conditions best – patients.

To find out more, Deep Dive caught up with Amy Abernethy, chief medical officer at Verily, to discuss the need for longitudinal, holistic data in IBD research, and the importance of giving patients a seat at the table.

Data-powered research

At the forefront of Verily's work in the IBD space, is creating a multidimensional longitudinal registry for IBD patients, developed in partnership with the Crohn's & Colitis Foundation. The registry builds upon lessons learned by conducting the Baseline Gut Research Project – a pilot research effort launched alongside the Foundation in 2021.

As Abernethy explains, the pilot followed participants with IBD over time, collecting data such as patient-reported outcomes. Now, having 'stress-tested' the viability of working in collaboration with the Foundation, the partnership is looking to expand upon their previous work and establish an infrastructure to rapidly answer clinical research questions in IBD, accelerate treatment development, and ultimately improve quality of life for people living with these diseases.

"The pilot data was like the toe in the water," says Abernethy. "We were pressure testing a few different things. Are these the right data elements to be collected? Which patient reported outcomes are a low burden for people, but also provide meaningful information? What's the right educational activity for people?

"And now we're taking those lessons learned and saying, 'Okay, what should we do more of? What do we need to add new data elements in?'."

To create a more holistic representation of IBD, Abernethy explains that registry aims to gather patient data at different stages of their disease progression, providing a more comprehensive and contextual understanding of the information collected in clinical settings.

By compiling a detailed longitudinal record of patients' health experiences, it will be possible to investigate significant clinical research questions. Moreover, the inclusion of features such as symptom and quality-of-life tracking will be particularly valuable in understanding the efficacy and benefits of treatments for chronic conditions like Crohn's disease and ulcerative colitis. The registry data will be accessible to academic and industry researchers who can collaborate on the design of prospective studies or use the data for observational studies, and this information will be available through Verily's clinical research suite and IBD Plexus, the Foundation's current data platform.

Abernethy notes, “One plan is for longitudinal data collection inclusive of patient-reported outcomes, longitudinal clinical data, and then also the ability to build into progressively more complex data sets the data types, such as environmental exposure data, and information about the explicit treatments and care a person with IBD receives and how that happens across time.”

“But then, there’ll be intermittent interactions with the person to ask questions, such as symptoms, like belly pain and other concerns, quality of life, as well as the impact on daily things that matter, like being able to go to work or care for your children. So, really trying to understand both personal experience as well as life impact and then following those things over time.”

Moving towards patient-focused care

When approaching the subject of IBD data, it is difficult not to think of the adage ‘trust your gut’. On the surface, this may be a tricky task for those with ulcerative colitis or Crohn’s disease. However, when it comes to building a truly patient-focused data registry that reflects the real lived experience of IBD, listening to the patient’s gut may actually be a highly valuable resource.

“IBD is inherently longitudinal, chronic, and burdensome in a person’s life,” explains Abernethy. “And so, being able to collect data directly from people living their real lives is very much in line with the kinds of solutions that Verily is building.”

This is not simply a passive experience for participants, she continues. Through the registry, patients have an avenue to directly contribute to research simply by sharing information about their health.

"We have a core belief that supporting patient advocacy and supporting patient communities is one way of supporting health and patient-centric precision health, because it's not only a trusted community, but also patient communities know what people need," explains Abernethy. "You've got the ability to aggregate an understanding of here's what matters most, which may not be obvious. And so, that's one of the things that we're really excited about, the Crohn's and Colitis Foundation relationship, because we think that they know the IBD community. We don't want to presuppose that we understand it better."

She continues, "There will be times when we'll have to cross-check and say, you know, 'Amy, it says that you went to the hospital last week. Is that true? It seems like you were there for three days. Is that accurate?' Because the individual is the best person to cross-check information."

Working towards precision treatment

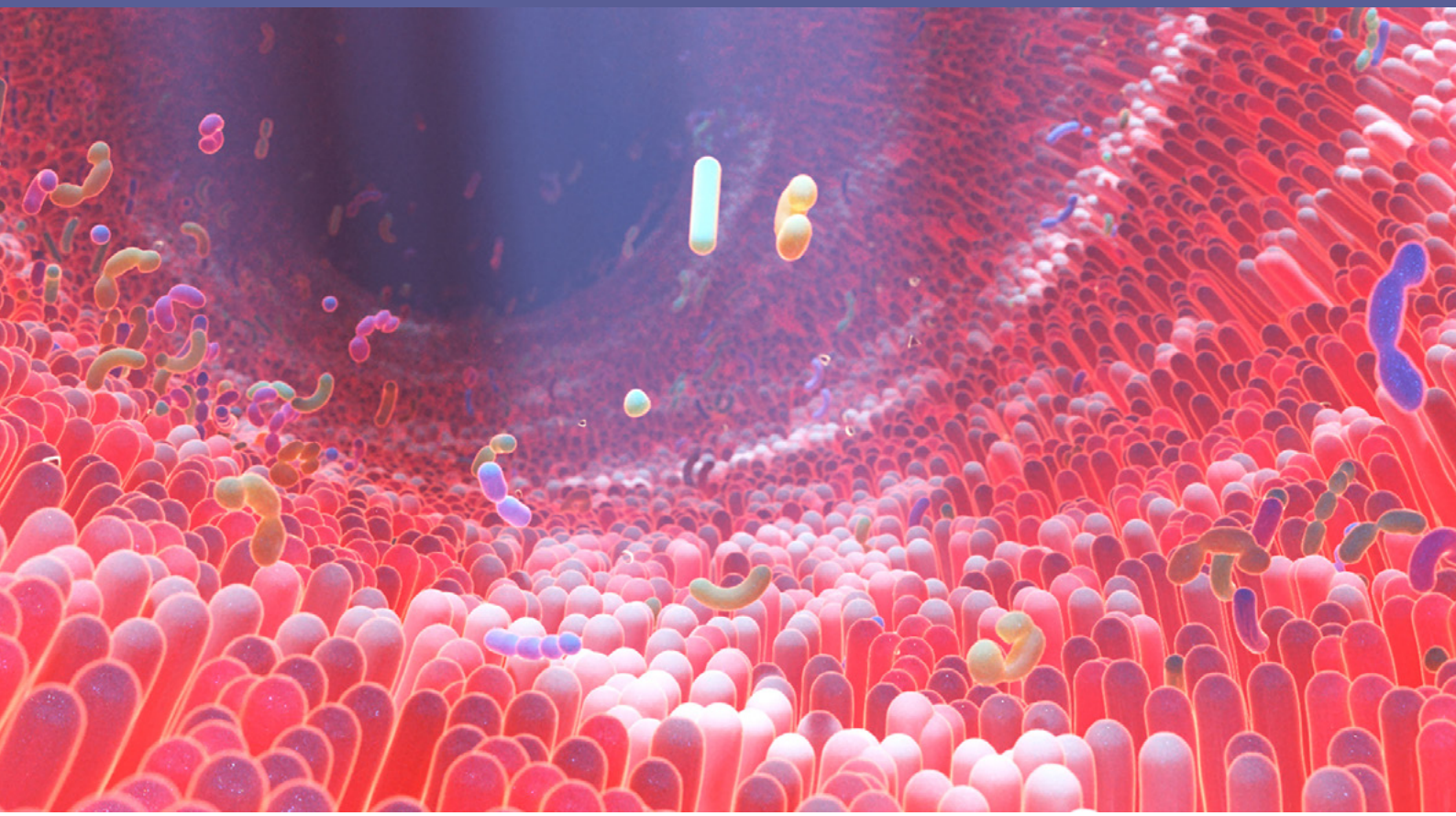
Research into gut health and IBD has escalated significantly in recent years. Around the world, conditions such as ulcerative colitis and Crohn's disease have become notable topics for public health discourse. In parallel, the prevalence of these conditions, alongside their substantial research and treatment potential, have made IBD a prime target for scientists and drugmakers.

Combining the genetic and lifestyle information provided by the patient with data from other sources, such as health records, creates a greater pool of information for researchers to draw from. As Abernethy highlights, there are still many unknowns when it comes to IBD, its causes, and the best way to treat and prevent flare-ups, but with the aid of longitudinal, real-world data, researchers can begin to identify patterns and relationships that were previously unexplored. This information can be used to develop personalised interventions that target the specific factors contributing to an individual's gut health issues.

"You can also take a cut of the data and do an exploration of environmental exposure risks and outcomes in IBD so that you can, with patients' or people's permission, also recontact people for new clinical trials that might be appropriate for them because they've got inflammatory bowel disease," says Abernethy. "There are blunt instruments and blunt scales right now, but they are not very precise, and it makes it hard to do clinical trials and drug development in this space, despite how badly it's needed. So, you know, all of these things argue for patient-centric models with longitudinal data where multimodal data types are actually going to make a lot of difference, and where the patient advocacy space can really help move things forward."

About the author

Eloise McLennan is the editor for pharmaphorum's Deep Dive magazine. She has been a journalist and editor in the healthcare field for more than five years and has worked at several leading publications in the UK.



Plotting the way forward on clinical trial diversity

As the old adage goes, the first step towards solving a problem is admitting you have one. For pharma's clinical trial diversity problem, that first step was a monumental undertaking, but in the last few years, it's one that seems to have been cleared. The next steps won't be easy either. Making clinical trial diversity the status quo will require flexibility, accountability, collaboration, and an openness to new ways of thinking about trials. To find out more, we spoke with experts from across the industry who are doing the work to learn what it's going to take to make real progress.

Clinical trial diversity has been gaining currency, at least as a talking point, for the last several years. And, most would agree, it's about time.

"We've been doing trials the same way for five decades," Christopher Boone, AbbVie's vice president and global head of health economics and outcomes research, told pharmaphorum in an interview last year. "Truly, the exact same way. So, if there's any area that's ripe for disruption, I would say clinical trials are it."

Like so many other industry disruptions, the recent prominence of clinical trial diversity work seems to have been pushed along by COVID-19, which disproportionately affected racial minority communities, as well as nationwide protests in the United States after the killing of George Floyd by police in Minneapolis in 2020.

"When the George Floyd murder happened, and the civil unrest in America happened, right around when we were in the throes of lockdown, it forced, not just Moderna, but the industry and the world overall to pause and take a look at what those racial inequities were and how we as an organisation and organisations across the globe needed to address them," said Jameka Hill, senior director of clinical trial health equity at Moderna.

That reckoning gave way to pledges and reports and eventually an FDA guidance later that year. This has been followed by further guidance and even legislation: a 2022 omnibus funding bill signed into law late last year by US President Joe Biden included provisions requiring companies to submit diversity action plans for phase 3 drug studies and device studies.

"I think that with the omnibus that came out through the legislature at the end of 2022, it's really applying more pressure to pharma to say, like, this is not only an ethical responsibility of yours, it's a scientific and a medical responsibility," Medable CEO Michelle Longmire told pharmaphorum. "We need to have more diversity in the clinical trials."

Non-representative trials that don't match the populations that interventions will be used in are a scientific concern, as well as an ethical one, as Longmire points out, because they affect the validity of the research, particularly when it comes to how treatments work in the excluded groups. But clinical trial diversity is also an equity issue, because, increasingly, clinical trials of new therapies are the best option available for treatment. And if that option isn't available to a certain subgroup of the population, then their outcomes will suffer.

Ricki Fairley, founder and CEO of TOUCH Black Breast Cancer Alliance, shared her own experience – in which she survived triple negative breast cancer with a two-year prognosis because of experimental drugs – in a recent DiMe webinar.

"As I started my advocacy, I looked back at the history of the drugs that were standard of care [for triple negative breast cancer] and there were no black women in those trials," she said. "Black women under 35 get breast cancer at twice the rate and die at three times the rate of white women, well before they would have that first mammogram at 40. We don't have the drugs that would work most effectively because they were never tested on black bodies."

So, what is being done so far to increase trial diversity, and what still needs to be done?

Getting away from the same old sites

Research sponsors never set out to run 80% white trials. The lack of diversity in clinical trials has arisen from systemic factors. For instance, pharma companies have historically liked to work with the same large, academic medical centres when it comes to trial sites – centres that have well-honed operational procedures, comfortably large patient bases, and an existing, low-risk relationship with sponsors.

Liz Beatty is chief strategy officer at Inato, a tech company that has developed a marketplace model to help connect smaller community sites to large sponsors. But the early days of that project were eye-opening, she says.

"What we realised rapidly was that no matter how much data we put in front of sponsors, around a wide range of research centres, they still pick the same sites they've always worked with before," she said. "You already know how to contract with them. You already know something about their budget. Even operationally, there's less risk because you've worked with them before."

Many interventions have focused on de-risking and cost-consciously scaling the prospect of working with smaller sites that are more tied to the local community. Inato's model is predicated on creating a two-way marketplace where community sites can actively woo sponsors, as well as being vetted to some extent by the platform.

Some pharma companies have simply taken the plunge to identify and work with these community centres themselves.

"At Moderna, when we are designing our clinical trials, we do so with inclusion in mind," Hill said. "We select sites with the representation of the community in which we're looking to serve and where the intended audience is in mind – as opposed to traditionally what's happened is it's kind of first come, first serve basis, right? You bring on the sites and the research facilities that, you know, historically have done a good job and they then bring in the participants from whatever background as quickly as possible."

And this desire for diverse sites has brought whole new players into the market – players like CVS, Walgreens, and Walmart, which have all launched clinical trial groups in the last three years.

"Combating, working towards, and frankly, doing away with this notion of lack of diversity in clinical trials, it's been a core part of the mission here and integrated into pretty much everything that we do," Dr Owen Garrick, chief medical officer of clinical trial services at CVS Health, told pharmaphorum. "So, we got involved as a company with recruiting, identifying subjects for the COVID vaccine studies, and in those situations, we were extremely successful in helping the sponsors at that time increase the diversity of the participants. And that really prompted the enterprise to think about expanding more broadly and more thoroughly into clinical trials."

Awareness and trust

Community sites are important not just because of demography but also because of the human challenges of clinical trial recruitment – which is to say, to get people into a clinical trial, they need to be aware of clinical trials, and they need to trust in the institutions carrying them out. This can be a tall order for communities that have been historically mistreated in the name of clinical research.

Awareness, at least, has increased in the wake of COVID-19.

"More people are aware of clinical trials for no other reason than what they saw and experienced during the pandemic and getting vaccines," Abbvie's Boone said. "So, layman's understanding of clinical trials, I would say, is at an all-time high. And that sort of nets out a greater interest, curiosity, and hopefully participation in clinical trials."

Trust is a harder nut to crack than awareness. One surefire way to garner trust, however, is to let people hear about clinical research from people who look like them.

"Who an individual receives their information from matters, especially in minority communities— it's about trust and who's going to keep me safe," Hill said. "And we have found, and the data has proven that … especially in minority communities, if that individual is a person of colour, the trust increases, which also means likely that the retention increases, and our attrition rate decreases."

Inato's Beatty adds that these community sites are just better equipped, often, to have the kind of deep conversations that engender trust.

"Some of our sites in our research centres in the community actually have very deep ties to certain subpopulations, and they know that community very well. In and out. Those are the people they serve every day," she said. "So, they know how to approach the conversation. They know how to involve their families. They know that sometimes you have to sit down, serve coffee or tea, and have a longer conversation, because those are the types of relationships that matter long-term in a very important healthcare decision."

The importance of flexibility

COVID-19 spurred a rise in decentralised trials, utilising telemedicine and sensors, as well as home visits. And while it's a separate trend from the push for diversity, there's no doubt that they're related.

Essentially, decentralised trials increase access and make participation easier for people who might be hampered by socio-economic factors that are often correlated with membership in a minority population— not having reliable transportation, not being able to take time off work to come into a clinical site, or not having access to childcare, to name a few.

"We want to try and look at ways that we can decrease that burden," Hill said. "Can you go to your local pharmacy in order to have some of your follow-up visits as opposed to having to travel for two hours? Can we leverage telehealth? Can we even cut down on the overall number of visits? I mean, I think, as researchers, we're always trying to gather more and more and more information, but we have to temper that with, well, what's actually necessary that doesn't increase the burden to those participants."

Just being in those community sites goes a long way toward improving that access, as Beatty and Garrick pointed out, and technology can go even further. All of this is important because retention is just as important as recruitment for truly diverse treatments.

"You don't want patients of any kind dropping off, but you want to make sure that a lot of the work that you spend in terms diversifying those that are recruited doesn't go to waste, and they are part of the data set that is available at the end of the trial," Garrick said.

Ultimately, every patient and every patient experience is different, so if you want to retain patients, you have to give them flexibility and optionality.

Curebase's vice president of clinical trial innovation, Jane Myles, paraphrased Acclinate CEO Del Smith, who gives a good illustration.

"His example is, and he tells his story better than me, lots of people who are underrepresented in trials think of their home as a sacred space. All the things out in the world are hard, I have to overcome things out there, and when I go home, it's my place. And so, his point is, not everybody wants to invite people in from the outside world to their place. You can't assume that by adding mobile nursing visits, you're going to meet the needs of those underrepresented people," she said. "What you want to do, and what's hard right now for trial teams, is build parallel workflows. Like, okay, if you want to go to the site, you can do that. You want to do this at home, you can do that."

The way forward: Measurement and collaboration

Inato works with a variety of different pharma companies. Beatty said that there's a range when it comes to dedication to the work.

"We see a wide variety of engagement and strategic focus on this topic. Some are really trying to be forward-thinking. It's a problem they want to be a part of solving and a really critical part of their clinical trial strategy. Others are trying to figure out how we will do it," she said.

Patient choice, trust, access, and shifting the locus of trials to community sites are all promising paths forward for clinical trials. But how can the industry writ large codify these best practices and make sure they become standard across the board?

Just before this story went to press, the Digital Medicine Society (DiMe) launched a DEI toolkit for digitised clinical trials, working with a number of industry stakeholders including several pharma companies to create the resource – and example of the kind of collaboration that will be needed going forward.

One aspect where industry collaboration will be key will be in standardising benchmarks and measurements, so everyone can get on the same page about what's working and how much progress is being made.

"We have really shifted the paradigm of how we conduct our trials so that now every program we run has a rigorous kind of checkpoint of, okay, are the sites selected with inclusion in mind? What are the demographics that we're leaning into?" Hill said. "Because, like with anything, if you don't know where you're headed and you're not measuring it, you never know if you're succeeding."

Internal measurement – which is to some degree now being mandated by the FDA guidance – is a first step, but cross-industry conversations will be essential.

"We realise that even if we solve this with all of CVS's patients, we touch a third of the population," Garrick said. "There are still another two-thirds of the population that we don't currently serve on a regular basis. So, we will, one, share the roadmap, frankly, because we think it serves US public health. Secondly, we'll also engage with regulators at FDA and other places as FDA begins to implement some of the policy from recent legislation around, say, having a diversity plan as part of your research, what that could or should look like, and we can give some examples of what has worked well and what hasn't worked well."

Ultimately, it will take collaboration between pharma sponsors, research sites large and small, tech solutions, and, of course, patients to reach the goal of diverse, representative trials.

"I think this is a really complex problem," Beatty said. "It's not going to be an easy solution that gets there."

About the author

Jonah Comstock is a veteran health tech and digital health reporter. In addition to covering the industry for nearly a decade through articles and podcasts, he is also an oft-seen face at digital health events and on digital health Twitter.

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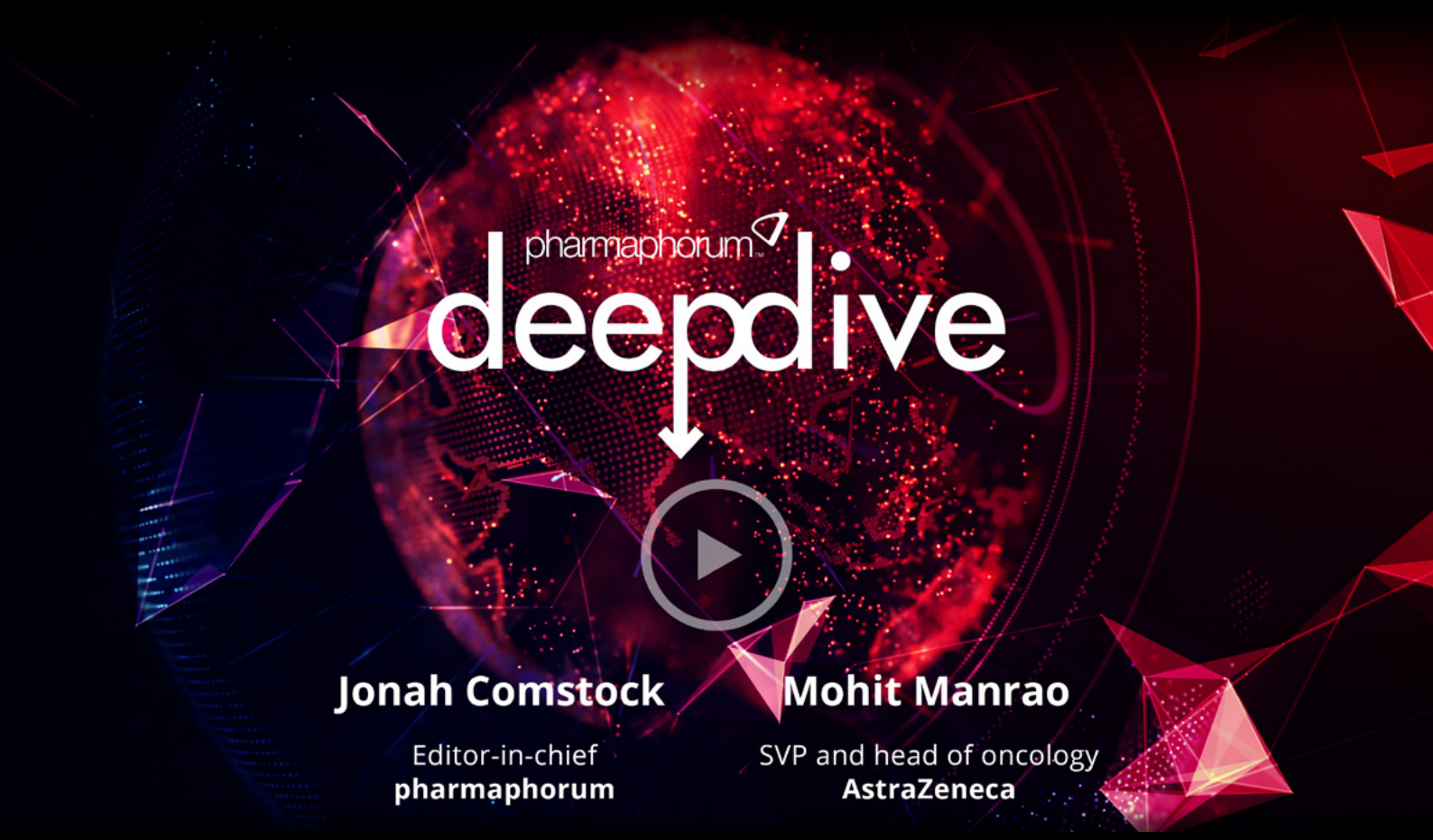
What's next for oncology research?

Eliminating cancer as a cause of death is a highly ambitious goal, but oncology researchers are showing no signs of giving up the fight in 2023. To find out more, pharmaphorum editor-in-chief, Jonah Comstock sat down with SVP and head of oncology at AstraZeneca, Mohit Manrao, to discuss key oncology trends for 2023, and AstraZeneca's ongoing work to eradicate cancer.

Check out the full interview to learn more:



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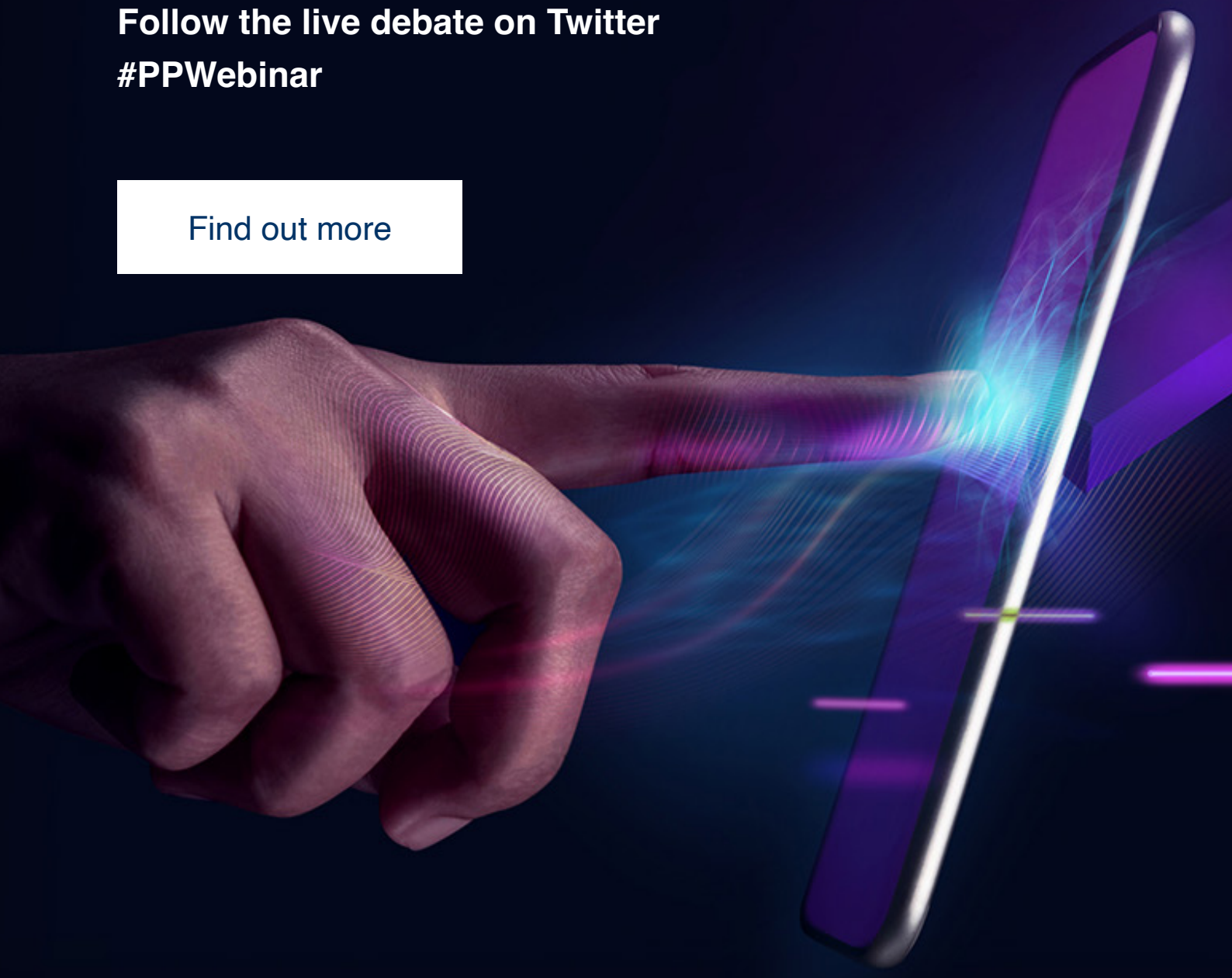

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Heard on the pipeline: R&D in the pharma industry

In the fast-paced world of healthcare, it can take a lot of work to keep up-to-date with the numerous innovations, trends, and opinions that emerge each year.

And so, to cut through the noise of information, when the Deep Dive team caught up with attendees at the J.P. Morgan Healthcare Conference, we kept things simple.

One question: What are the biggest pharma R&D trends to watch in 2023?

Here's what some of the best minds in healthcare had to say:

Raj Chopra

Acting CEO, Aethon Therapeutics

There's been a huge explosion of cancer discoveries, particularly in drug discovery. We've had small molecule inhibitors, we've now had targeted protein degradation, and then we've got the revolutionary use of antibody, both bispecific antibodies – we've just seen Genentech register a bispecific in lymphoma – and we've also seen antibody-drug conjugates coming through. I think this [our technology] is yet another pillar of the armamentarium against cancer.

Adi Hoess

CEO, Affimed

We have been talking about cellular therapies for many years. And despite the fact that there were some initial successes – we always have some low-hanging fruits – we're now in the phase of optimisation. Usually, that looks like: 'Here was a one-off success, but you have to wait another five or ten years to see the fruits coming through', and it takes a while until it's ripe. I think out of all the diseases out there, the most important one to address is cancer.

I can imagine that the trend in the future will be you bring together bispecifics, checkpoints, and cellular therapies as they become cheaper, but also the mRNA vaccines and technologies. Then you have a really good service for the patient. It can take care of the tumour by itself, and also, the threat is taken away from the family, where you don't know if the cancer is coming back.

Alexandre LeVerte

Chairman and CEO, Osivax

One of the trends is that the funding market is putting a lot of pressure on biotech, so we need to be creative about how to ensure that we can still aggressively push forward on the projects that are needed. There's a lot of money around, but it's just not allocated as it used to be. I think 2022 and 2023 have been really different, with the historical shareholders supporting their companies in a much stronger way and probably M&A coming into play to balance this. The market relied on new rounds of funding two years ago. Now, it's time for the maturation of this whole ecosystem.

Michelle Longmire

CEO, Medable

We're in a golden age of science. When you look at the progress of mRNA – this is a technology we've been working on since the 60s, but suddenly its application has become something so profound, with so much potential. As we know, though, the clinical trial remains the bottleneck. Thirty-seven drugs were approved last year. The average is around 50. First, why fewer? And second, why have we only had the same rough number of approvals for ten years? Clearly, in a golden age of science, we should be able to see more shots on goal, ideally, and therefore more approvals without lowering any standards.

I see the awesome leverage of technology and innovation in basic science and pre-clinical development. But I don't see that same innovation and technology applied to clinical development. I think the data we're showing to bend the cost curve is really suggestive of a new era, but we need that same kind of leverage of technology that we see in pre-clinical to be applied to the clinical process. That's how we unlock not 50 but 500 drugs approved.

As awesome as the science is, we don't get cures until we solve this problem.

Gerry Chile

Newell Health (Healthware)

If we want to talk trends, almost like fashion trends or the coolest, hottest thing around, it's hard to get away from ChatGPT and what everyone's talking about. But certainly, artificial intelligence is going to be jumping out of the gate. It already has, probably three to five years sooner than I was expecting at this level. The floodgates have been opened with this public trial of ChatGPT; there are already health applications, it passed the medical exam, it passed the bar exam, it passed everything. When you sit down and play with it, you realise in your areas of expertise, it just cannot be trusted. But that's only scratching the surface.

While we're not doing anything with ChatGPT, certainly data science is a huge component of the Soturi project. It tries to build algorithms with predictive modelling, trying to make sense of data points from many different types of data sources. So, I think we are coming to a point where algorithmic, machine learning, data science-driven healthcare is really going to come of age starting this year into the next two to three years.

Robin Roberts

Novartis Biome

The pandemic created an interesting scenario where digital health, in general, became incredibly important. It allowed folks from across our industry to overcome this learning curve that they wouldn't have necessarily wanted to push against, which got them to the point where they're using these digital health solutions and now are seeing the value of utilising them. I think 2023 is going to be one of the first years where we are going to have to do everything we can to keep as much of that momentum as we possibly can within our industry and across the healthcare system.

When we deliver healthcare, telehealth is just a part of the way we do business. What other value-add can we incorporate into that capability that makes it even more valuable? It's one thing to be able to talk to your physician on video. It's another thing if they collect the metrics they need during that video call and make diagnoses. The technology is out there. It's not a technology issue. We're talking about using technology that has been available for decades and applying it to the right use cases in the healthcare space.

Gene Kinney

President and CEO, Prothera Biosciences

We're very focused on these protein-based diseases, and we think the field, in particular in Alzheimer's disease, is at a very exciting inflexion point, and it's happening right now. We're seeing the first two anti-amyloid treatments receive accelerated approval, first Biogen's molecule and then the Eisai molecule.

We have more data sets coming. We'll have another accelerated approval decision coming from the FDA around Eli Lilly's molecule in the space. And then we'll see, we've already seen Phase 3 data sets at scientific conferences, but now we'll see the review of that from the FDA and then reimbursement decisions coming from CMS and others. So, we're excited to see how this space continues to evolve, and there are a lot of inflexion points around that.

Jim Joyce

CEO and co-founder, Health Beacon

For me, the two R&D trends that we want to try to figure out are this GLP-1 market, so this whole market where a broader scale of consumers that suffer from weight and underlying metabolic issues are now being introduced to this really exciting new class of medications, GLP-1s, and we don't know how that's going to impact. And the other one is what's happening in the cancer space around mRNA vaccinations and targeting. I think we're going to see continued trends there.

Joe Spinelli

SVP product and strategy, AccessDx Laboratory

Generally speaking, pharma programmes increasingly do not live in a silo. It's more about understanding underlying disease conditions, looking through risk analysis, and then helping to effectively manage and improve insights for how these things can be delivered effectively.

That last mile concept of how therapies can actually be effectively used and utilised is something that's really important and continues to be a big opportunity for both proactive identification for where a therapy could be beneficial, but also to see it through to understanding all the other extenuating circumstances.

Lisa Yañez

Chief operating officer, Aerami Therapeutics

What I'm seeing in particular, given the nature of what's happening right now in the markets, I think people are doubling down on what they know. From an R&D perspective, we've probably taken less of a risk in terms of the opportunity that we see with this [Aerami] programme. We're probably going to hold off a little on some of our earlier potential platform opportunities to make sure that we get it right.

It really forces you to prioritise and right-size, which is good. It's good for shareholders, and it's good for patients. I hope that the markets get better and that, looking forward, we can be a little nimbler and a little more provocative and things like that. But as a realist, I think it's a little different than the last 10-15 years that I've been working in clinical development within rare disease. It's basically more choiceful.

James D. Lechleiter

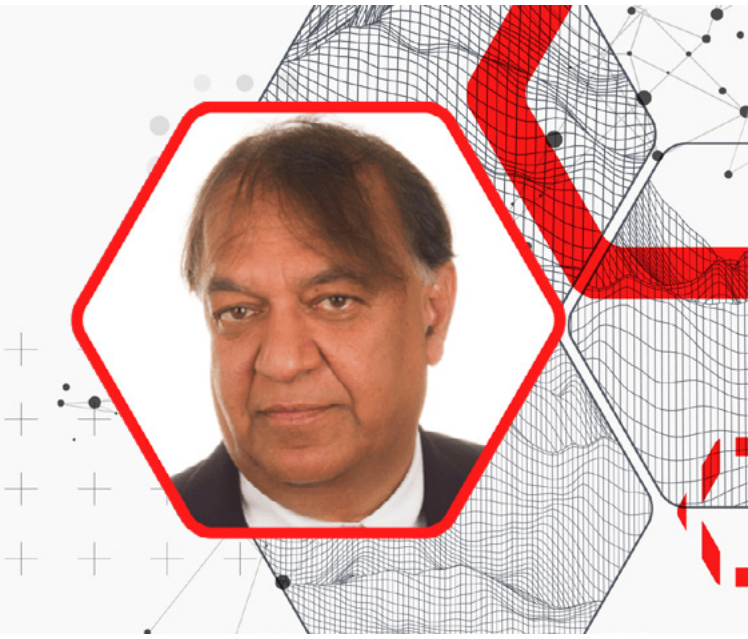
Co-founder and chief scientific advisor, Astrocyte

I actually think neuroscience, in general, is an area where no one's found any good treatment options. Opportunities in that space, neurodegenerative disease, stroke, trauma, that's actually a really incredible opportunity because there's been so little that's been successful. That's a big trend.

Now, how that's going to be done – that's another question. We think the trend is going to be taking a second look at this if you haven't been. If you've had it on the back burner, let's take a look at the neuroscience space and see whether or not there's something we can actually work with there.

Ravi Anand

Chief medical officer, Newron



With the seriousness of the health crises, I think we'll see many trends with regulators, academia, industry, citizens, and disease awareness groups, all collaborating very closely and helping expedite the procedures by which new treatments can be developed marketed.

For instance, I think you see a great collaboration in the ELS space. You see it in multiple sclerosis. Groups are being formed, and new treatments are being evaluated much more rapidly than ever before. So, I think we're not going to make a fundamental breakthrough in 2023 in the kind of medication, but more in the way we cooperate with each other.

About the authors

Eloise McLennan is the editor for pharmaphorum's Deep Dive magazine. She has been a journalist and editor in the healthcare field for more than five years and has worked at several leading publications in the UK.

Jonah Comstock is a veteran health tech and digital health reporter. In addition to covering the industry for nearly a decade through articles and podcasts, he is also an oft-seen face at digital health events and on digital health Twitter.

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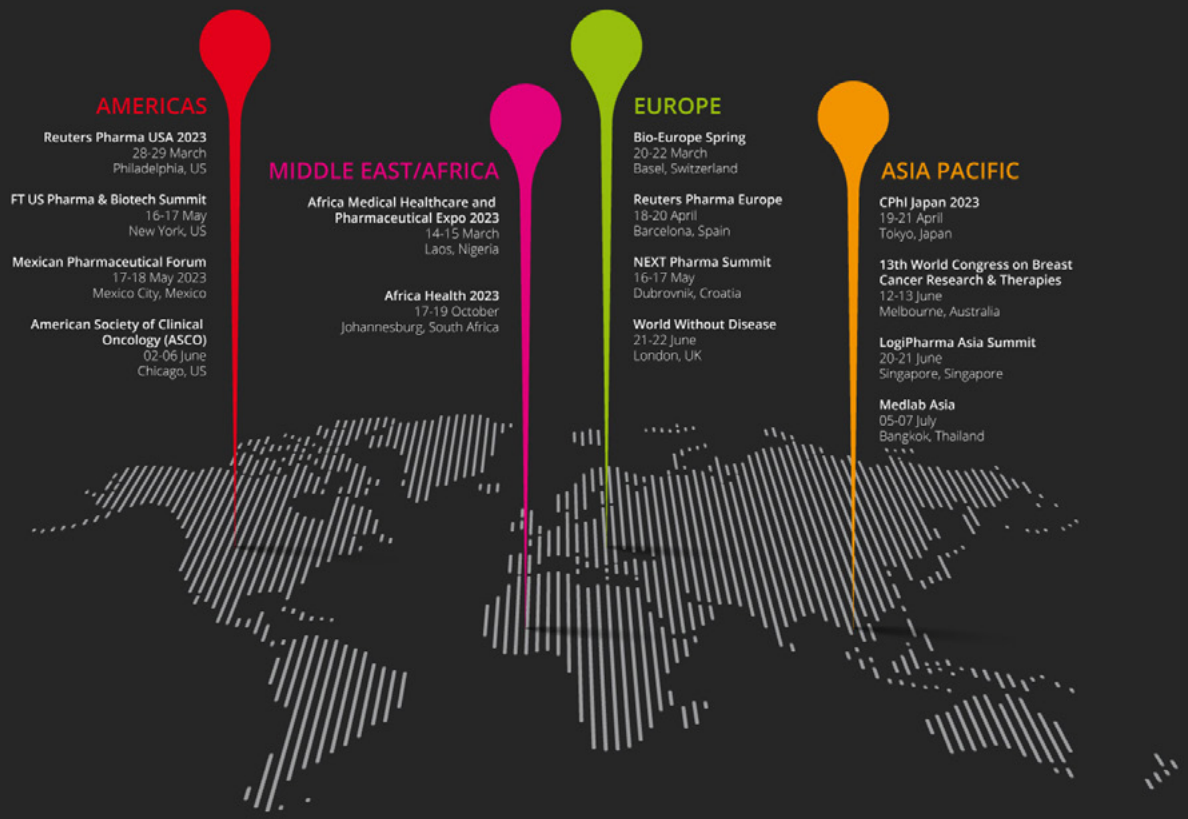

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Reuters Pharma USA 2023
28-29 March
Philadelphia, US
Event details

FT US Pharma & Biotech Summit
16-17-May
New York, US
Event details

Mexican Pharmaceutical Forum
17-18 May 2023
Mexico City, Mexico
Event details

American Society of Clinical Oncology (ASCO)
02-06 June
Chicago, US
Event details

Middle East/Africa

Africa Medical Healthcare and Pharmaceutical Expo 2023
14-15 March
Laos, Nigeria
Event details

Africa Health 2023
17-19 October
Johannesburg, South Africa
Event details

Europe

Bio-Europe Spring
20-22 March
Basel, Switzerland
Event details

Reuters Pharma Europe
18-20 April
Barcelona, Spain
Event details

NEXT Pharma Summit
16-17 May
Dubrovnik, Croatia
Event details

World Without Disease
21-22 June
London, UK
Event details

Asia Pacific

CPhI Japan 2023
19-21 April
Tokyo, Japan
Event details

13th World Congress on Breast Cancer Research & Therapies
12-13 June
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Contacts

Editorial team
Eloise McLennan
editorial@pharmaphorum.com

Sales team
Matthew Brookes
advertising@pharmaphorum.com

Design
Mike Hammerton
Mike Smith

A pharmaphorum media publication

www.pharmaphorum.com

pharmaphorum media ltd, Third Floor, Rosemount House, Rosemount Avenue, West Byfleet, Surrey KT14 6LB, UK
Tel: +44 (0)1932 339 264