Technology Networks

The Scientific Observer

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To The Depths of Drug Discovery

How Artificial Intelligence Is Advancing Structural Proteomics

—

How Can BioPlatforms Support the mRNA "Revolution"

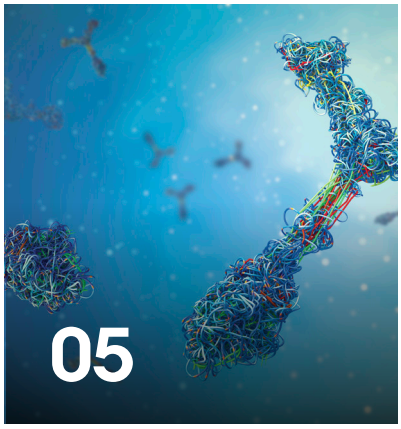
CONTENT

FEATURE

To The Depths of Drug Discovery

Molly Campbell

COVER IMAGE: Isabella Fassler



EDITORS' NOTE

Welcome to issue fourteen of *The Scientific Observer*, the monthly online magazine brought to you by *Technology Networks*.

Highlights from the newsroom this month include a study suggesting a link between modern-day seasonal flu and the 1918 pandemic strain, and the development of an injectable hydrogel shown to enhance CAR T-cell therapy for solid tumors.

In an interview with Dr. Marlena Fejzo, Kate Robinson investigates hyperemesis gravidarum – a disorder causing severe nausea and vomiting during pregnancy – and how a gene variant known as *GDF15* could be implicated in the condition.

For our feature this month, Molly Campbell takes a deep dive into the treasure trove of secondary metabolites present in the ocean and how the therapeutic potential of marine-derived natural products is being harnessed. With insights from Professor William Gerwick, a leading figure in pharmacognosy, the development of therapeutics including antivirals and drugs to treat cancer is explored as well as emerging applications such as neurological diseases.

In our dedicated vaccines section, Francina Agosti discusses how bioplatforms are supporting the mRNA revolution. As well as looking at the role bioplatforms played in the development of SARS-CoV-2 vaccines and how they can enable rapid adaptation to emerging variants, we hear how the technology is helping to drive advances in personalized medicine and cancer vaccines.

We hope you enjoy exploring this issue of *The Scientific Observer*. Subscribe to make sure you never miss an issue.

Have an idea for a story?

If you would like to contribute to *The Scientific Observer*, please feel free to email our friendly editorial team.

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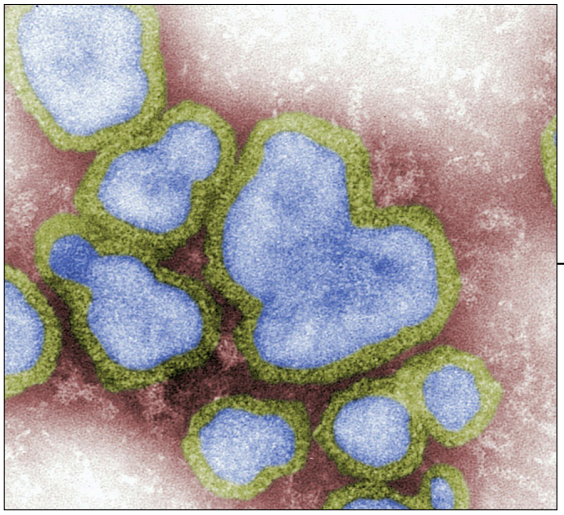
From the Newsroom

COULD BREW METHOD – AND GENDER – BE LINKED TO COFFEE'S ASSOCIATION WITH INCREASED CHOLESTEROL?

MOLLY CAMPBELL

A new observational study has explored the effect of coffee consumption on serum total cholesterol (STC) levels in adult populations. The research team also collected data on how different brewing methods affect STC, discovering an association that differed across sexes.

JOURNAL: *Open Heart.*

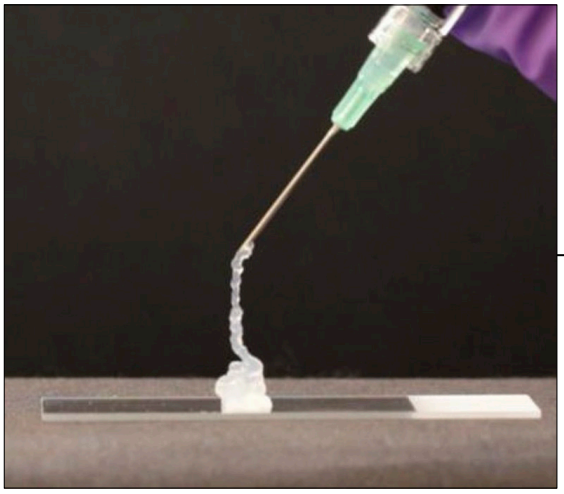


SEASONAL FLU MAY BE DESCENDED FROM THE 1918 PANDEMIC STRAIN

RUAIRI J MACKENZIE

A new study has characterized samples of the influenza virus that ravaged the world's population in 1918, highlighting a link between that viral strain and modern-day seasonal flu.

JOURNAL: *Nature Communications.*



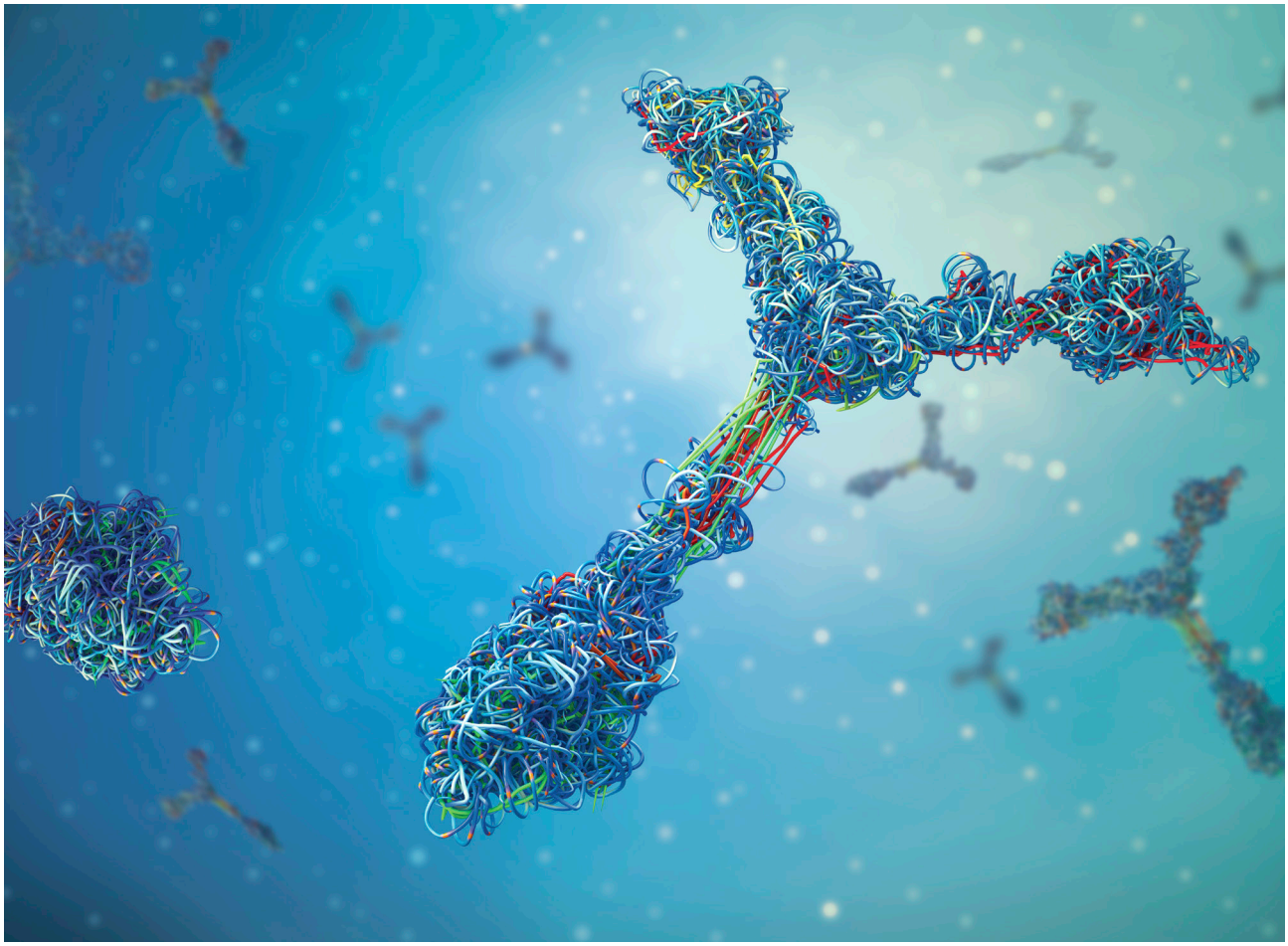
CAR T-CELL THERAPY HYDROGEL CURES CANCER IN MOUSE MODELS

MOLLY CAMPBELL

Engineers from Stanford University have created an injectable hydrogel that can be loaded with immune cells to enhance CAR T-cell therapy for solid tumors.

JOURNAL: *Science Advances.*

CDC, Abigail K. Grosskopf.



How Artificial Intelligence Is Advancing Structural Proteomics

ANNA MACDONALD AND MOLLY CAMPBELL

This article is based on research findings that are yet to be peer-reviewed. Results are therefore regarded as preliminary and should be interpreted as such. Find out about the role of the peer review process in research here. For further information, please contact the cited source.

Understanding protein complex formation is crucial in drug design and the development of therapeutic proteins such as antibodies. However, proteins can attach to each other in millions of different combinations and current docking solutions used to predict these interactions can be very slow. Faster and more accurate solutions are needed to streamline the process.

In a pre-print published earlier this year, a new machine-learning model – EquiDock – was introduced that can rapidly predict how two proteins will interact. Unlike other approaches, the model doesn't rely on heavy candidate sampling and was shown to reach predictions up to 80—500 times faster than popular docking software.

To learn more about EquiDock and how artificial intelligence (AI) methods are advancing the field of structural proteomics, *Technology Networks* spoke to co-lead author of the paper, Octavian-Eugen Ganea, a postdoctoral researcher in the MIT Computer Science and Artificial Intelligence Laboratory.

Molly Campbell (MC): For our readers that may be unfamiliar, please can you describe your current research focus in proteomics?

OCTAVIAN GANEA (OG): My research uses AI (specifically, deep learning) to model aspects of molecules that are important in various applications such as drug discovery.

Proteins are involved in most of the biological processes in our bodies. Two or more proteins with different functions interact and form larger machines, i.e., complexes. They also bind to smaller molecules such as those found in drugs. These processes change the biological

functions of individual proteins, for instance an ideal drug would inhibit a cancer-causing protein by attaching to specific parts of its surface. I am interested in using deep learning to model these interactions and to assist and speed-up the research of chemists and biologists by providing better and faster computational tools.

attachment happens by trying out all possible combinations and rotations.

MC: Can you explain how you created EquiDock?

OG: EquiDock takes the 3D structures of two proteins and directly identifies which areas are likely to interact, which otherwise would be a complicated problem even for a biology expert. Discovering this information is then enough for understanding how to rotate and orient the two proteins in their attached positions. EquiDock learns to capture complex docking patterns from a large set of ~41,000 protein structures using a geometrically constrained model with thousands of parameters that are dynamically and automatically adjusted until they solve the task very well.

MC: What are the potential applications of EquiDock?

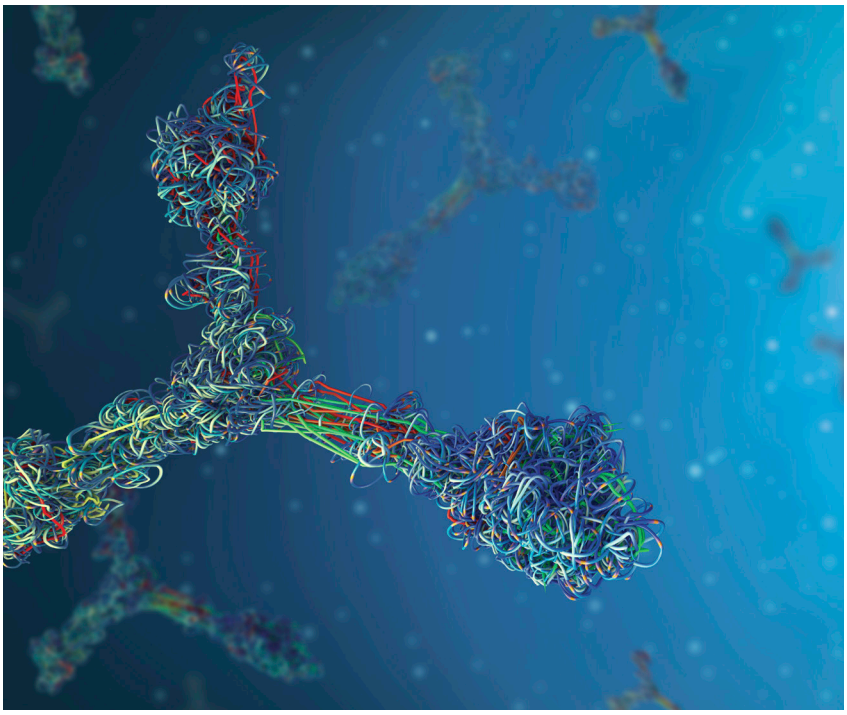
OG: As already mentioned, EquiDock can enable fast computational scanning of drug side effects. This goes along with massive scale virtual screening of drugs and other types of molecules (e.g., antibodies, nanobodies and peptides). This is needed in order to significantly reduce an astronomical search space that would otherwise be infeasible for all our current experimental capabilities (even world-wide aggregated). A fast protein-protein docking method such as EquiDock combined with a fast protein structure prediction model (such as AlphaFold2 developed by DeepMind) would help drug design, protein engineering, antibody generation, or understanding a drug's mechanism of action, among many other exciting applications critically needed in our search for better disease treatments. ●

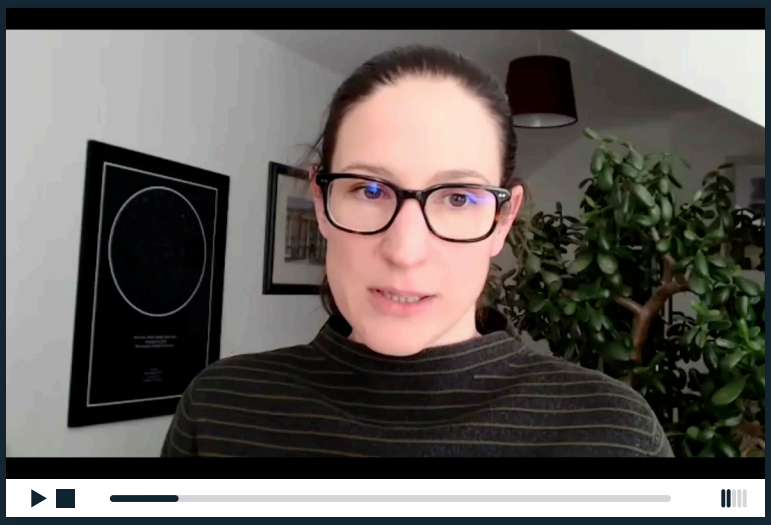
Octavian Ganea was speaking to Molly Campbell, Senior Science Writer for Technology Networks.

"Proteins are involved in most of the biological processes in our bodies."

MC: How are AI-based methods advancing the field of proteomics and specifically structural proteomics?

OG: Biological processes are inherently very complicated and have their own mysteries, even for domain experts. For instance, to understand how interacting proteins attach to each other, humans or computers have to try out all possible attachment combinations in order to find the most plausible one. Intuitively, having two three-dimensional objects with very irregular surfaces, one has to rotate them and try to dock them in all possible ways until one can find two complementary regions on both surfaces that would match very well in terms of their geometric and chemical patterns. This is a very time-consuming process for both manual approaches and computational ones. Moreover, biologists are interested in discovering new interactions across a very large set of proteins such as the ~20,000-sized human proteome. This is important, for instance, for automatically discovering unexpected side-effects of new treatments. Such a problem now becomes similar to an extremely large 3D puzzle where one has to simultaneously scan pieces for matching ones, as well as understand how each single pairwise





Everything You Need To Know About Vitamin D

WITH DR. LINA ZGAGA

For this issue of *The Scientific Observer*, our feature *Teach Me in 10* is brought to you by Dr. Lina Zgaga, associate professor in public health and primary care at Trinity College Dublin.

In just 10 minutes, Dr. Zgaga talks us through what vitamin D is (plot twist, it's actually a hormone, not a vitamin), why it's important in human health and some of the key challenges in vitamin D research. ●

Teach Me in 10 is a video series brought to you by LabTube, part of the *Technology Networks* group. We invite scientists to present and summarize their research, or a scientific concept, in less than 10 minutes.

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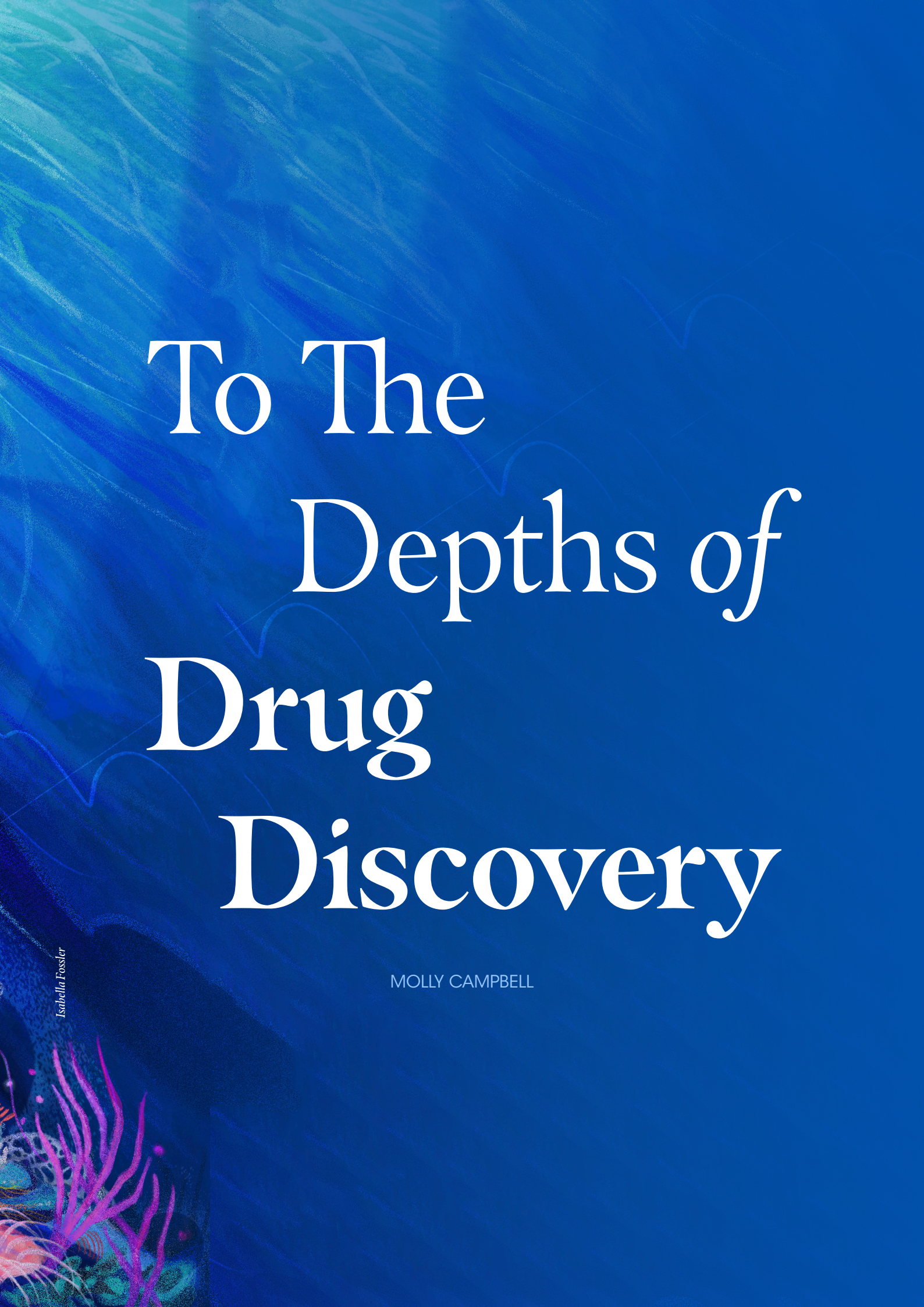
To The Depths of Drug Discovery

MOLLY CAMPBELL



Isabella Fossler

The ocean: Earth's "cradle of life", home to some of the greatest biological and chemical diversity found on our planet. Throughout the history of our existence, humanity has relied on the ocean as a source of oxygen, food, exploration, creativity and vitality. Over recent decades, a "new wave" of marine natural products research has emerged, demonstrating how the ocean may also be key in our fight against human disease.

Join us on this feature-length voyage to the depths of drug discovery.

NATURAL PRODUCTS IN MEDICINE

There are certain intrinsic biological processes that occur in living organisms that are essential for development, growth and reproduction. Examples are the synthesis and breakdown of nucleic acids, proteins and fats. Collectively, these processes are referred to as primary metabolism, and the subsequent products, primary metabolites.

Living organisms are also capable of making molecules *outside* of primary metabolism. Secondary metabolites – often used interchangeably with the term natural products – are biosynthesized via secondary metabolism, which describes processes that are "an expression of the individuality of a species," as Dias, Urban and Roessner describe in *A Historical Overview of Natural Products in Drug Discovery*. Secondary metabolites are not essential for an organism's survival, but require energy to produce, and therefore often confer an advantage for the organism to thrive in its particular habitat. Secondary metabolites may be the product of a biological defence mechanism or a process an organism has developed for nutrient acquisition, as examples.

Natural products have been harnessed for their therapeutic properties throughout the history of medicine. Land-dwelling – or terrestrial organisms – such as plants and soil microbes have naturally dominated the focus of scientists wanting to access nature's pharmacopeia.

But an untapped resource of natural products, large in size and potential, was close by – we just couldn't access it.

A NEW WAVE IN NATURAL PRODUCTS DISCOVERY

Marine-derived natural products – secondary metabolites obtained from organisms of the ocean – have been utilized by humans for an array of different purposes. An ancient civilization – the Phoenicians – inhabited the coastlines of the Mediterranean Sea thousands of years ago. Sometimes referred to as "the purple people" these civilizations harnessed the secretions of a mollusc species found in abundance in the shallow shores – *Murex brandaris* – to produce a long-lasting purple dye.

The *therapeutic* potential of marine-derived natural products, particularly those from easily accessed fish and algae, was perhaps recognized early in the early twentieth century, but wasn't demonstrated scientifically until much later. The advent and popularization of SCUBA marked the beginning of a "new wave" in natural products discovery, as scientists journeyed to unexplored regions and depths of the ocean.

"The origins of marine-derived natural products really stem back to the days when chemists were also SCUBA divers, or had an interest in the ocean," says Professor William Gerwick, a distinguished professor in the Skaggs School of Pharmacy and Pharmaceutical Sciences and the Scripps Institution of Oceanography at the University of California San Diego (UCSD). Gerwick, considered a leading figure in natural products chemistry and pharmacognosy, has received numerous accolades for his contributions to natural products research.

"Really, the chemistry aspect was what drove the early days of questioning, 'What's out there? What are the potential materials being produced?'" he says.

As researchers were able to venture deeper into the ocean, and collect samples of increasingly smaller size, they uncovered many novel compounds with interesting structures. "Basically, everything that you picked up had new chemistry in it. So, there was this amazing period of people finding lots of interesting new structures and studying the biological properties of these molecules, Dr. Paul Jensen, a professor at the Scripps Institution of Oceanography, UCSD, describes in a recent podcast, *Marine Science*.

The "new chemistry" being discovered was a form of communication.

A SIGHTLESS, SOUNDLESS WORLD

It's estimated that between 70,000–100,000,000 different marine species exist, ranging from the gloriously gigantic blue whale (~ 33 meters in length) to macroscopic marine bacteria (~ 1,000 nm in size). This number may be even higher, Gerwick says, "largely on the basis of so many bacteria being observed by DNA sequencing technologies."

In the face of harsh environmental pressures, marine life has been forced to develop unique traits that aid survival. Some are physical, structural or behavioral. But largely, the language of the ocean is chemical, as Gerwick elegantly describes: "In the sightless and soundless world of most underwater life, the mechanism of communication by ocean creatures is through their chemicals."

Take crustaceans for example. For many species, mating only occurs within a specific period, once the mature females have molted (a process where the hard outer layer of the shell is shed). Male crustaceans can detect the upcoming molting period via chemical signals produced by the female. This allows the males to "guard" the female until she is ready to mate. Research has shown that, when rocks and sponges are treated with female urine – which carries the compounds involved in this chemical signaling – male crustaceans will do their very best to attempt mating with the rock, or sponge.

Phytoplankton are microscopic marine algae that are central to the ocean's

Murex brandaris, a mollusc species that was utilized by the Phoenicians to produce a purple dye.

"The origins of marine-derived natural products really stem back to the days when chemists were also SCUBA divers, or had an interest in the ocean," says Gerwick.

balanced ecosystem. Colonies of the phytoplankton *Phaeocystis globosa* are vulnerable to attacks by other marine organisms. Copepods – small crustaceans – can consume whole colonies of the phytoplankton, whereas ciliates choose to consume only single cells. When copepods start to attack *P. globosa,* the phytoplankton can chemically detect that the attack is occurring, and that it is by copepods, rather than ciliates. As a result of these chemical signals, colony formation is suppressed, such that the phytoplankton grow as individual cells, too tiny for the copepods to attack.

Symbiotic microbes also have a role in the chemical communication of the ocean. Many marine organisms live in association with other micro and macroorganisms to enable their survival. For example, the shrimp species *Palaemon macrodactylus* carry embryos externally, on the abdomen. Scientists from the laboratory of Professor William Fenical, regarded as a "true pioneer" in the field of marine natural products chemistry – and Gerwick's PhD mentor – discovered that symbiotic microbes covering the surface of the embryos produce a metabolite: 2,3-indolinedione (isatin). This metabolite functions by protecting the embryos from pathogenic marine fungi.

"In the sea, creatures are bathed in essentially a salty soup, filled with microorganisms and viruses with which they have intimate contact, but somehow, they seem to survive. This is a result of the rich suite of adaptive chemicals that they produce," says Gerwick.

It's this chemical language – and its rich diversity – that makes the ocean a treasure trove for secondary metabolites. Historically, terrestrial organisms had proven to be a valuable source of natural products that possess medicinal properties. Would this be reflected in the planet's waters?

"Scientists found marine invertebrates such as sponges, corals and even snails produce molecules with significant pharmaceutical relevance," Dr. Vikram Shende, a postdoctoral fellow in Professor Bradley Moore's lab at the Scripps Institution of Oceanography, explains. Shende studies the biosynthesis of secondary metabolites by marine eukaryotes and their associated microbes.

MARINE-DERIVED DRUGS AUTHORIZED FOR HUMAN USE

During the 1990s, the field really experienced a sense of intensification,

both in terms of interest and sophistication, Gerwick describes. Emerging techniques and technologies – such as next-generation sequencing – evolved to new heights of speed and sensitivity, with lowering costs. Scientists could study the complexity of marine organisms at a new level of detail, gaining insights into the role of specific genes, encoding proteins, metabolic pathways and the subsequent molecules produced. "There was a realization that there really are drugs out there [in the ocean]. Or, if not drugs themselves, molecules that could inspire the production of a drug," Gerwick recalls. Investments from large research organizations and "Big Pharma" further fuelled the search for therapeutics from the sea.

Fast-forward to 2022, and a growing number of marine-derived natural products have progressed to authorization for human use or are in clinical trials. The exact number of marine-derived (or inspired) compounds authorized is a little unclear and varies depending on whether a source cites global or region-specific authorizations. Gerwick believes that the total figure is currently 23. "I'm not quite sure why some people exclude certain drugs from the list, such as those used in China to treat millions of patients, or some of the various fish oil products, or even the anticancer agents based on arabinose sugars. I think our list of 23 is the most comprehensive at the present time," he says.

Authorized marine-derived drugs are of various chemical classes, including peptides, alkaloids, nucleosides, fatty acids, oligosaccharides and antibody-drug conjugates. Some are synthesized by marine organisms themselves, while others are inspired by the chemical structures of secondary metabolites produced by marine organisms. Let's explore a few examples.

Several drugs authorized to treat cancers are derived from different species of molluscs and/ or symbiotic bacteria. Brentuximab vedotin (brand name Adcetris®), for example, is an antibody-drug conjugate authorized to treat lymphomas. "This drug uses an antibody to target tumor cells and deliver a small molecule 'warhead' based on a peptide molecule, dolastatin 10, isolated from a sea hare," explains Kayla Wilson, a graduate student in the Moore lab at the Scripps Institution of Oceanography. Interestingly, the sea hare does not actually make this compound, but acquires it from its diet of marine cyanobacteria (blue-green algae).

Fatty acids extracted from fish, such as Omega-3-carboxylic acid (brand name Epanova®) and Eicosapentaenoic acid ethyl ester (brand name Vascepa®), are authorized for the treatment of hypertriglyceridemia, a common condition characterized by increased levels of serum triglycerides that can contribute to the development of cardiovascular disease.

Many bioactive compounds have also been extracted from sea sponges. "Sea sponges are fascinating to researchers from several different areas of science. Evolutionary biologists study them to learn how early animal life evolved on earth, materials scientists use them to build bioinspired scaffolds, and we as natural products chemists study them because they make medicines," says Wilson.

Acyclovir, one of the first systemic antiviral medications to be approved by the US Food and Drug Administration (FDA), was heavily inspired by nucleosides isolated from a Caribbean sponge, *Tectitethya crypta* (formerly known as *Cryptotheca crypta*). The cancer medication Eribulin (brand

name Halaven®), used to treat breast cancer and liposarcoma, is a synthetic form of halichondrin B, a compound first isolated from the *Halichondria okadai* sponge. Subsequent research identified that this compound is produced via a symbiotic relationship with bacteria. Indeed, this has been the case for many bioactive compounds extracted from sea sponges.

"Sponges have a complex microbiome – just like we have a complex human microbiome – and dozens of biologically active molecules have been discovered," Wilson says. However, recent work by Wilson's colleagues at the Moore lab, focusing on the terpene-producing sponge *Axinella*, suggests that the sponges themselves can synthesize many interesting compounds. Using long-read DNA sequencing, Wilson and team looked at the genes surrounding terpene synthases, enzymes critical for the production of terpenes. "These surrounding genes contained introns and had large non-coding regions between them – which are both characteristic of eukaryotic DNA," she explains. The data imply that the sponge is the synthesizer of terpenes, not the bacteria that constitute its microbiome. This work demonstrates the constant evolution of our understanding of natural product synthesis.

SERVING UNMET NEEDS IN DRUG DISCOVERY

The list of authorized marine-derived drug examples provided is by no means exhaustive, but perhaps demonstrates the broad landscape of clinical applications and sources of these therapeutics.

An interesting aspect of the field is how marine-derived natural products could offer a sense of renewed excitement for disease areas that currently lack efficacious treatments. An example is neuroscience drug discovery, where a high-profile "retreat" from research and development by Big Pharma has left an unmet clinical need for many patients.

"Unfortunately, several costly failures have led pharmaceutical companies to largely exit neuroscience drug development over the last couple of decades, which has occurred as increased lifespans and increasing numbers of patients with neurological disorders leads to a large gap in what is needed vs. what is being done," explains Dr. Marsha Pierce, an assistant professor at Midwestern University. Pierce's research focus includes studying the role of oxytocin analogs, marine natural products in drug development and microRNAs in sensorineural development, function and maintenance.

Could marine-derived natural products offer neuroscience drug discovery an opportunity for revival? It's possible, and some success has already been had. In 2004, the FDA approved the analgesic Ziconotide (brand name Prialt®) – a synthetic version of the ω-conopeptide found in the venom of a giant marine snail, *Conus magus* – for the treatment of chronic pain.

Many other marine organisms produce toxins, either as a defence mechanism, or – if they are predators – to paralyze their prey prior to eating them. The target of several such toxin classes are voltage-gated ion channels, key mediators in a wide range of central and peripheral nervous system functions in humans, such as neuronal excitability and inhibition.

For Pierce, a key area of unmet clinical need, where marine-derived natural products could carry potential, is in the treatment of ischemic stroke: "There are no current pharmaceutical therapeutics for post-stroke recovery beyond the acute blockage-treating phase," she says.

Post-stroke, the affected brain region demonstrates dynamic changes in excitability, new research suggests. "There is a period of recovery with characteristic heightened neuroplasticity in the peri-infarct region," says Pierce. "However, this increased cortical excitability and plasticity is opposed by increases in tonic GABAergic inhibition." Methods to prevent this opposition could enhance the potential for new synaptic connections to form, repairing the damaged brain region.

"Marine natural products from organisms and their symbiotic microorganisms display unique chemically active primary and secondary metabolite structures that are very different from those in synthetic chemical libraries," – Pierce.

In 2020, Pierce and colleagues published a research project that examined whether Brevetoxin-2 (PbTx-2), a voltage-gated sodium channel modifier obtained from marine dinoflagellate *Karenia brevis*, could drive cortical excitability and promote neuronal plasticity in mice after a stroke. The research team showed that, in mouse models, epicortical application of the toxin resulted in increased neurite outgrowth and

connectivity that corresponded with improved physical functioning.

"For neurological diseases, we've had few breakthroughs with the current synthetic chemical libraries largely because they work by generating derivatives of already existing compounds. In my opinion, it is the extreme conditions of marine organisms and unique structures of marine bioactive compounds that open the door for novel drug discovery," says Pierce.

FROM SEA-BED TO PATIENT-BED: CHALLENGES AND RECENT ADVANCES

Drug discovery and development is a nuanced area of scientific research that faces many bottlenecks, whether compounds are synthetically or biologically synthesized.

Shende speaks to the particular difficulties associated with natural products: "It's definitely a long road to take a molecule from nature and get it into something that people will use every day," he says. "Along with the traditional challenges of getting a drug into clinical trials, a big consideration especially for molecules from marine organisms or their microbiomes is supply. These organisms can be extremely slow growing, and in some cases rare or even endangered, so trying to harvest enough material for something like a clinical trial is not only economically unviable but can also be environmentally harmful."

Despite these challenges, marine-derived drug discovery and development has demonstrated a respectable track record of bringing drugs to patients. Perhaps this can be attributed to the field's enthusiasm to evolve? "One dimension of marine-derived natural products research that I think has been particularly positive is that it has continued to stay current and relevant. It's adopted new technologies, new thinking and new research goals," he says.

A notable example is the introduction of artificial intelligence (AI)-based methods, which Gerwick has been working on in collaboration with computer scientist Gary Cottrell and his students at UCSD.

Discovering and developing bioactive compounds from marine organisms is a process for which the methods vary between laboratories. Generally, methods can be characterized as either top-down – which Gerwick describes as a chemistry-driven process – and a bottom-up approach, which could be argued as being "more DNA-driven".

Marine-derived drug discovery and development has demonstrated a respectable track record of bringing drugs to patients.

"We use both approaches in my lab," says Gerwick. "The top-down approach really starts with accessing the organism. We typically go on expeditions to various tropical locations where we scuba dive and collect samples. We store these samples to bring home, and we also try to take small samples that we may be able to grow in the laboratory." He paints a visual picture of his laboratory, adorned with several hundred different strains of marine cyanobacteria of varying colors.

Organic solvents are used to extract compounds from organisms in the laboratory, which are then subjected to a variety of biological assays to search for useful activities. This could be anti-cancer activity, antiviral activity or antiparasitic activity. "When we find an extract or a fraction that shows activity, we then do further refinement to get to the actual active compound in that material using chromatography," Gerwick adds. "These things are easy to say. But it can take weeks to months to years to accomplish. Once we get a pure compound, then we want to figure out what it is."

The next step requires various spectroscopic techniques to study the size, orientation and arrangements of the atoms. It also stimulates a lot of new questions that, as Gerwick describes, can occupy a lifetime – or perhaps more than a lifetime – of further study.

That's where AI-based programs, like the deep learning of NMR spectra called Small Molecule Accurate Recognition Technology (SMART), can help. "I see our use of AI in this field as a way to enhance and accelerate that process of figuring out what a new molecular structure is, or to enhance and figure out what the target of a compound is," Gerwick says. "We're also developing some AI software that would enable you to take a new molecule and predict what biological activity it might have – could it have anti-cancer potential, and to what type of cancer would it be effective?"

He emphasizes that AI doesn't necessarily give us solutions, but it helps to create hypotheses that need to be taken into evaluation. However, an essential requirement for AI – and a potential bottleneck here – is a need for good quality data from which you can train the system. This is a current shortcoming, according to Gerwick.

If this shortcoming can be overcome, AI looks set to "make waves" in marine-derived drug discovery, and natural products research more generally: "A process that used to take weeks to months now can be done in eight seconds. We're still working on the technology, but the dream is that [it] will really make a difference in the efficiency of the process," Gerwick emphasizes.

THE IMPACT OF CLIMATE CHANGE AND BIODIVERSITY LOSS

Natural products as drugs will continue to be a critical – if not increasingly important – aspect of human health care. But success in natural products discovery is intrinsically linked with thriving biodiversity, and the planet is facing a biodiversity crisis.

The rate of species extinction on Earth is estimated to be 10–100 times higher than it has been over the last 10 million years, and only continues to rise. The catastrophic impact of this decline in biodiversity can be seen in terrestrial organisms, but also in marine life.

In April, researchers published a report in *Science* exploring extinction risks for marine species using ecophysiological modeling. The study data suggest that, if the "business-as-usual" global temperature continues to increase, it is likely that marine systems will undergo mass extinction on a similar level to the end-Permian extinction (EPME), in which ~80% of marine biodiversity was lost.

A threat to marine biodiversity is of course a threat to marine-derived natural products, explains Pierce: "Adaptation to their unique habitat contributes to marine organisms and their symbiotic microorganisms producing a wide variety of biologically active primary and secondary metabolites," she says. "Climate change is leading to a rapid loss of marine organism abundance and diversity, as well as the symbiotic microorganisms inhabiting many of these marine organisms and producing some of these bioactive structures." If a species disappears, we will never know what it had the capacity to produce.

Natural product discovery and development cannot continue in a sustainable manner without efforts to tackle biodiversity conservation. Global and local efforts are ongoing here. "Partnering biodiversity preservation with drug discovery has been a long-standing focus of the International Cooperative Biodiversity Groups (ICBG) program of the Fogarty International Center, the international arm of the National Institutes of Health (NIH)," says Gerwick.

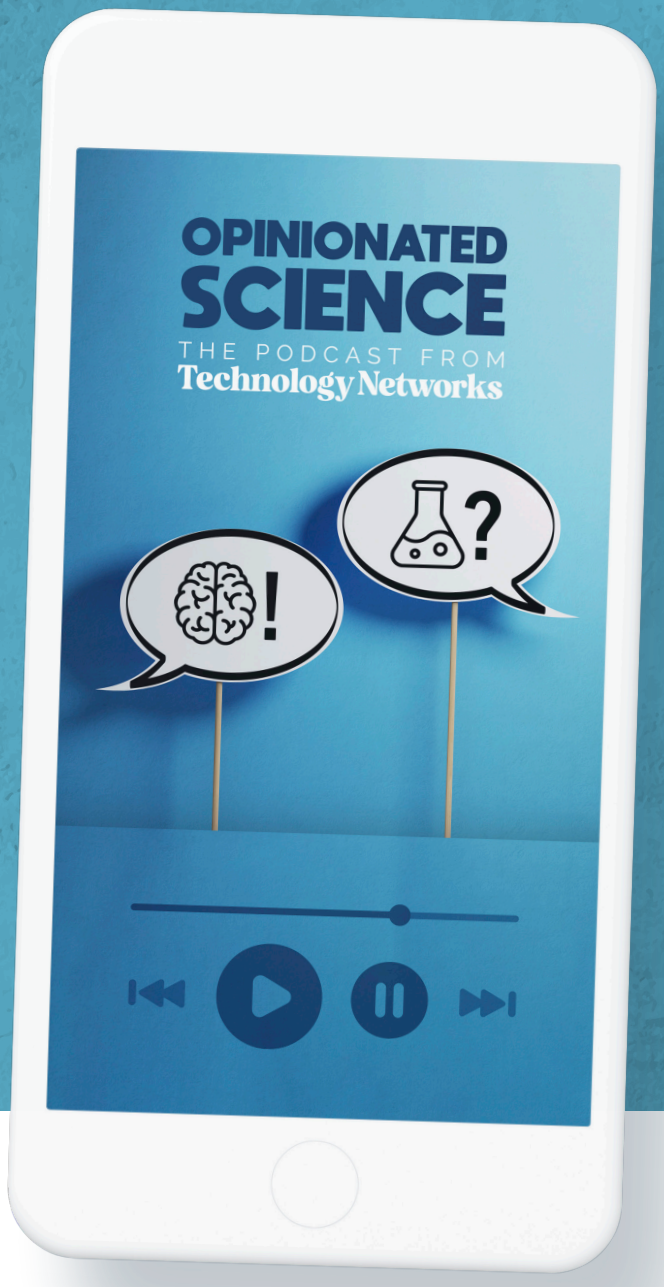
THE FUTURE OF THE PHARMASEA

Over the last few decades, the efficacy of marine natural products as therapeutics has been demonstrated against a wide variety of human diseases. The growing preclinical and clinical pipeline of marine-derived drugs points to a bright future for this fascinating field of research, and we're likely only just scratching the surface.

Humans have mapped a greater percentage of the Moon's surface than we have the seas of our planet; we can't possibly foresee the full extent of chemical diversity living within this vast, underwater realm. As for the future, the integration of sophisticated technologies – such as AI – and continued collaboration across a wide variety of scientific disciplines will no doubt elevate the study of marine natural products to new heights.

All the while, we must maintain – and bolster – our efforts to protect Earth's biodiversity. "I hope that by discovering new medicines from the marine environment, we can show the public why they should care about protecting the ocean," says Wilson. "The technologies we have to explore the chemistry and DNA of marine organisms are rapidly expanding and if we can keep our marine ecosystems healthy, it will be really exciting to see what we can learn in the coming decades."

Her thoughts are echoed by Gerwick: "As rich as this field is with promise for drug discovery, I think it's even richer in capacity for human development and understanding our planet" – this, he explains, is his mantra. ●



Genomics Power Hour: Decoding Morning Sickness and Dog Behavior

On this episode of *Opinionated Science*, the team reviews two studies that show off the power of genomic technologies, from very different angles. One answers key questions about why some women experience extreme vomiting and sickness in their first trimester of pregnancy, and the other reveals why dog breeds aren't all they are cracked up to be.

Opinionated Science is *Technology Networks*' homemade podcast, where our team of scientists-turned-journalists serve up slices of the weirdest and most fascinating stories from the world of science.

Find *Opinionated Science* on all major podcast platforms, including Apple Podcasts and Spotify.

Why Nausea and Vomiting During Pregnancy Might Not Just Be Morning Sickness

KATE ROBINSON

Morning sickness is common in pregnancy, with up to 80% of pregnant women experiencing this symptom at some point, however, if the nausea and sickness is excessive and accompanied by an inability to keep food down, you might not be experiencing morning sickness.

Hyperemesis gravidarum (HG) is the medical name for this rare condition, and University of Southern California Researcher Marlena Fejzo, PhD has experienced it firsthand, tragically miscarrying as a result. Fejzo was part of a team that made the first link between a gene variant known as *GDF15* and HG, and is working to bring attention to the disease and improve available diagnostics and treatment options.

Technology Networks had the pleasure of speaking with Fejzo to find out more about what women with HG currently face, the finding that HG may have a genetic cause and the possible future outcomes of this research.

Kate Robinson (KR): Can you tell us about your experience with HG and why research such as yours is so important?

MARLENA FEJZO (MF): I had HG and was treated with 7 different medications, but nothing worked, and I couldn't move without vomiting or keep anything down for 10 weeks. Every waking moment I had to lay completely still with extreme nausea. It was torture and ultimately, I was given total parenteral nutrition, but it was too late, and I lost the baby at 15 weeks' gestation.

Ever since then I have been researching HG to try to find answers, so people

don't have to go through what I did. It's been over 20 years and mothers and their babies are still suffering and even dying in the United States and around the world from HG. In addition, I and others have now shown that the saying "the baby gets everything it needs from mom" is false in the case of HG. A recent study found HG is associated with the highest risk (5-fold) of having a baby born small for gestational age – this is higher than exposure to cannabis, chronic hypertension, pre-gestational diabetes, preeclampsia, autoimmune disease, cocaine use, amphetamine use and tobacco use in pregnancy. HG is also associated with an increased risk for preterm birth, neurodevelopmental delay and autism spectrum disorder. Of note, HG has recently been shown to be associated with structural abnormalities of the brain. Adverse outcomes are not only limited to the offspring; mothers are at increased risk of suicidal ideation, post-traumatic stress and an array of long-term physical and social issues likely due to severe prolonged illness. Attention to this disease and progress are imperative.

KR: How is HG currently diagnosed and are there any treatment options available for the condition?

MF: HG is generally diagnosed as severe nausea and/or vomiting starting before 16 weeks gestational age, accompanied by an inability to eat and/or drink normally and inability to perform daily activities. It often leads to malnutrition, dehydration and weight loss. Treatment includes rehydration and prescription antiemetics. But current medications are not working well enough – the majority of patients do not gain any weight within two weeks of trying them. Importantly, patients who are unable to tolerate vitamins and are unable to eat properly should be administered thiamin to avoid a rare but serious complication of HG, Wernicke's Encephalopathy (brain damage caused by thiamin deficiency). Patients and providers also need resources and support, many of which can be found on the HER Foundation website at www.hyperemesis.org.

The immediate benefit of this research is that it provides clinicians and patients with an evidence-based cause of HG..." – Fejzo.

KR: Can you talk us through how you discovered that variants and mutations of the *GDF15* gene are linked to HG?

MF: In our study published in 2018, we partnered with a personal genetics company and performed a genome-wide association study comparing common genetic variants between 1,306 cases with HG and 15,756 controls. The greatest differences were found in variants around a gene that codes for a nausea and vomiting hormone called *GDF15*.

Recently, we performed a second genetic technique called whole-exome sequencing on a separate population of study participants, comparing common and rare variants within genes between 926 HG cases and 660 unaffected controls. In this study, the only gene that differed significantly between affected and unaffected individuals was *GDF15*. In addition, the only gene with a rare mutation in 10 or more people affected by HG was in *GDF15*. GDF15 is produced at high levels by the placenta in pregnancy and patients hospitalized with HG have significantly higher levels than pregnant patients with normal or no nausea and vomiting. This provides very strong evidence that *GDF15* is involved in the etiology of HG. While other factors may contribute, I would argue that there is now stronger evidence for *GDF15* causing HG than any other theory at this time.

KR: What implications do your findings have for individuals with HG?

MF: Patients are often dismissed or told that they are exaggerating symptoms, leading to undertreatment and pregnancy termination of wanted pregnancies. The immediate benefit of this research is that it provides clinicians and patients with an evidence-based cause of HG which validates the disease and will hopefully force providers and family members to take it more seriously. In the long run, it provides scientists and pharmaceutical companies with a novel pathway to pursue for prediction, diagnosis and treatment. Importantly, drugs targeting the GDF15 pathway are very effective in improving appetite and weight gain in animal models and are already in clinical trials in cancer patients. If safe, these new medications may benefit patients with HG, resulting in healthier mothers and babies.

KR: How will the strengths and limitations of this study guide future HG research?

MF: Future research should focus on the GDF15 pathway, rather than continuing to waste resources on outdated theories such as the pregnancy hormone human chorionic gonadotropin (hCG) or psychological factors. In addition, our recent study included subsets of patients of African, admixed American and East Asian ancestries, and has provided preliminary evidence that the results may be generalizable, but larger studies in these populations are needed to prove this. There is still much to be done to understand how the GDF15 pathway works in pregnancy and what other factors may be involved. Hopefully the knowledge gained can be used to develop tools for prediction, diagnosis and more effective treatments. ●

Dr. Marlena Fejzo was talking to Kate Robinson, Editorial Assistant for Technology Networks.

Blood-Based Biomarkers in Alzheimer's Disease

Lucy Lawrence

Identifying more sensitive biomarkers for Alzheimer's disease (AD) is an unmet medical need. It is key in the global efforts to validate disease-modifying AD therapeutics and identify appropriate recipients in clinical trials once more therapies are approved.

Fluid biomarkers are the most attractive tests for AD. However, there are challenges in developing blood biomarkers for neurological diseases with specificity, precision and reproducibility.

In this webinar, our expert speaker, Professor Lei Liu, assistant professor of neurology at Harvard Medical School, will discuss strategies for developing an ultrasensitive immunoassay to measure oligomeric amyloid β in human plasma precisely.

Professor Lei Liu

Assistant professor of Neurology, Brigham and Women's Hospital Harvard Medical School

WATCH NOW

Technology Networks frequently host educational webinars that span the breadth of our scientific coverage, from coronavirus to cannabis. Previous hosts include Nobel prize laureate Professor Jennifer Doudna and members of the team who pioneered the Oxford/AstraZeneca COVID-19 vaccine. You can view all of our latest webinars HERE.

How Can BioPlatforms Support the mRNA "Revolution"

FRANCINA AGOSTI

The science and medicine worlds are experiencing a new revolution, and this time the protagonist is the mRNA molecule. In this article, we explore why bioplatforms support this revolution.

HOW DID MRNA ARRIVE TO THE MEDICINE WORLD?

mRNA molecules have the power to direct a cell's function. mRNA is a code that, when read by a cell's machinery, creates a functional protein. Today, the potential use of mRNA in medicine is well recognized, but — as happens with many innovative scientific discoveries — that wasn't always the case. Dr. Katalin Karikó built her scientific career studying mRNA with the purpose of using it to treat human diseases. Since the 1970s, Dr. Karikó perceived mRNA's potential. But only after four decades of her struggling to get grants for research and laboratories to work in were her ideas widely recognized. In 2020, when the COVID-19 pandemic hit, the first mRNA-based vaccine was authorized for human use.

The mRNA revolution is not only based on the success of mRNA vaccines for COVID-19, but also the development of innovative cancer therapies using mRNA-based vaccines.

"Because of the COVID-19 vaccine success, mRNA is getting a lot of attention, but if we look at the history of mRNA technology, it started with cancer vaccine development," says Dr. Jinjun Shi, associate professor at the Center for Nanomedicine and Department of Anesthesiology, Brigham and Women's Hospital, Harvard Medical School. "Most of the design work that was being conducted for mRNA cancer vaccines was then applied to COVID-19 vaccines."

The development of mRNA-based vaccines or therapies relies on bioplatforms. One of the reasons COVID-19 vaccines were developed in a very short time is because bioplatforms for other infectious diseases — or cancer vaccines — were already established.

WHAT IS A BIOPLATFORM, AND HOW IT IS USED IN MRNA MEDICINE?

Bioplatforms involve special organizational and technological structures that biotech companies build to make their resources and technology reusable — and even cross-therapeutic. Ultimately, by making minor changes to a bioplatform in the drug discovery pathway, the development of new therapies for very different diseases can be achieved in a short time.

Take COVID-19 mRNA-based vaccines as an example. These vaccines deliver mRNA encoding the viral spike protein. By 2020, when the SARS-CoV-2 genomic sequence was known, some biotech companies working on mRNA vaccines for other diseases already had a bioplatform built. They were able to efficiently switch the specific spike protein mRNA sequence to use on their formulation. The rest of the drug discovery pathway was already implemented, like the mRNA manufacturing protocol, the cargo molecules to use, the delivery method and more.

Bioplatforms also provide a fast adaptation to changes. If the virus undergoes mutation — modifying its spike protein in a certain way such that the commercialized vaccines no longer prevent the disease — the bioplatform permits the development of a different vaccine against the new variant. A change to the mRNA to encode the new mutated sequence is all that is required. In this case, the vaccine development could be even faster, since clinical trials performed in humans to prevent COVID-19 infection already demonstrated vaccine safety, tolerability and efficacy, and explored important properties such as mRNA concentration, number of doses and delivery methods. This method is applicable to many viruses, not just SARS-CoV-2.

BIOPLATFORMS FOR FINDING A CURE FOR CANCER

mRNA technology is positioned to be used not only as a prophylactic for infectious diseases like COVID-19, but also as a therapeutic treatment for cancer.

In contrast to infectious vaccines, where knowing the viral DNA sequence is sufficient to develop a universal vaccine, for cancer mRNA vaccines it is necessary to sequence the DNA of the patient's healthy and cancerous cells.

The mRNA revolution is not only based on the success of mRNA vaccines for COVID-19, but also the development of innovative cancer therapies.

The comparison between the DNA sequences of healthy and cancerous cells determines one or more mutated proteins — or antigens — that are *only* found in the cancer cells. The mRNA in the cancer vaccine can be developed to carry the sequence of those antigens.

"There are a few critical things to take in consideration when switching from infectious disease to cancer vaccines," says Shi. "The first one is that we know the sequence of every viral protein, while in cancer it could be many proteins that carry mutations. The selection of the antigen(s) to use is critically important for the success of the cancer vaccine. To develop a successful cancer vaccine, you have to come with the right antigen, or even a few antigens, depending on the type of cancer to treat."

When the patient receives the mRNA vaccine, their immune cells start expressing the antigen and activate T cells. Then, those activated T cells kill

the tumor cells expressing those same antigens, fighting the cancer.

This kind of technology is a personalized therapy, since mutations could vary between patients, depending on the cancer type. A 2020 study applied DNA sequencing and tumor-infiltrating lymphocytes to identify specific mutations present in gastrointestinal cancer patients' tumors. Using this data, the research team developed a mRNA construct incorporating defined neoantigens, predicted neoepitopes and specific mutations of driver genes. The construct was administered to four patients and the immunological response observed. It was found to elicit mutation-specific T cell responses against the predicted neoepitopes.

Today, many other similar therapies are being tested in clinical trials. Bioplatforms are indispensable to developing personalized therapies, because once the bioplatform is in place and the technology is developed and tested for one particular case, then selecting the antigen(s) for each patient will be sufficient to develop the therapy for each individual.

MRNA-BASED THERAPIES FOR EVERYBODY

The COVID-19 pandemic highlighted the key difficulties that third-world countries face when accessing vaccines. As a result, the World Health Organization created the mRNA technology transfer hub.

The mRNA hub is a global bioplatform that shares knowledge and technology between low-income countries to help them produce state-of-the-art therapies for their population. The immediate goal is to develop mRNA COVID-19 vaccines to distribute among countries in need. As of April 2022, the WHO selected several low- and middle-income countries to take part in this collaborative project, including Argentina, Brazil, South Africa and South Korea, and there are plans to add more countries in the future.

The international and collective strategy that the mRNA hub is creating won't be limited to COVID-19 vaccines development. The hub plans to develop vaccines for other infectious diseases and cancers, making use of the mRNA bioplatform.

With bioplatforms, the process of developing and manufacturing safe and effective mRNA vaccines — either for infectious diseases or cancer — is extremely efficient when compared to manufacturing a classical vaccine from scratch. Bioplatforms allow mRNA technology to be transferable and reusable, accelerating the development of innovative vaccines. The mRNA revolution we are living in would not be possible — or at least *that* revolutionary — without the existence of bioplatforms. ●

Cell Culture Advances for Vaccine Development and Production

SOPHIE PROSOLEK

The COVID-19 pandemic has given rise to a number of scientific innovations, particularly in the production and testing of vaccine technology.

Since December 2020, a staggering 10 billion doses of SARS-CoV-2 vaccines have been administered worldwide – and while global vaccine equity remains a challenge to be overcome, some nations have even begun to experience SARS-CoV-2 vaccine surplus.

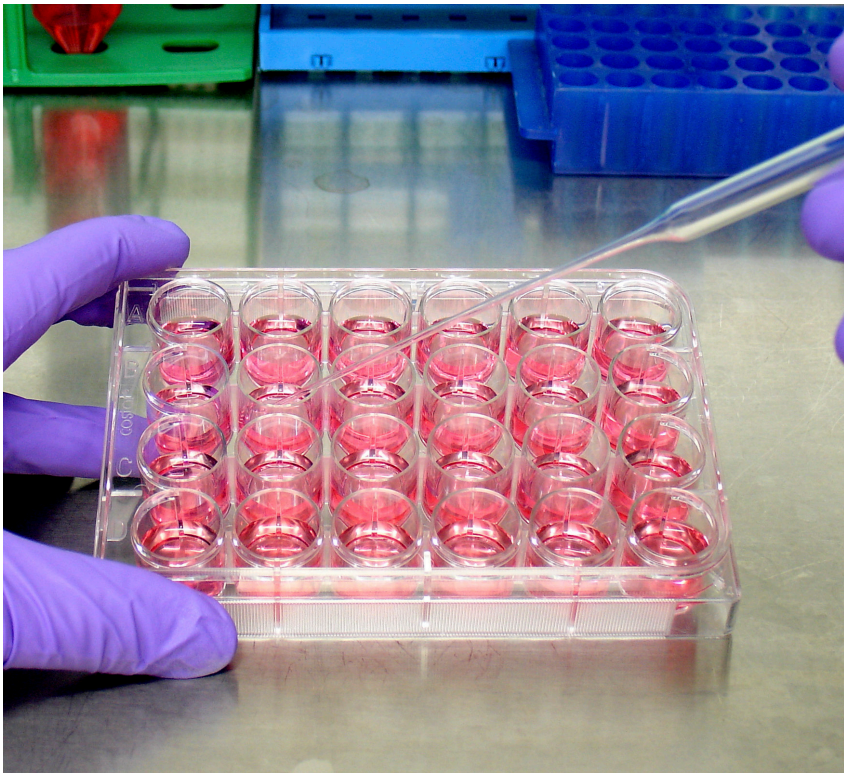
New and rapid production methods are carrying a record number of vaccines to clinics, a reality driven – at least in part – by the immunization demands of pandemic management and concurrent innovations in cell culture.

Cell culture – the process of growing cells outside of their natural environment under controlled artificial conditions – has been used widely in the development and testing of new vaccines since early methods were pioneered in the 1930s. Historically, vaccines have comprised either a whole or partial pathogen, inactivated for safe administration and grown within biological systems (such as chicken eggs or mammalian cells).

Today, the optimization of cell culture growth medium, the development of superior biological models and the reduced reliance on animal-derived components continues to drive the exciting and rapidly developing art of cell-based vaccine development.

CELL CULTURE IN EXPLORATORY VACCINE TESTING

Cell culture methods are instrumental in the exploratory, testing and production aspects of vaccine development. Vaccine candidates must be proven safe and effective in cell culture experiments before they can enter the preclinical stages of testing and production.



Due to the limitations of *in vitro* models, a high failure rate in preclinical and clinical trials continues to prove a significant bottleneck to vaccine manufacturing. Increasing the accuracy and reproducibility of cell culture models remains one of the biggest drivers of methodological innovation in vaccine development today.

ADDING ANOTHER DIMENSION TO VACCINE TESTING

In standard tissue culture practice, cells are grown in flat, two-dimensional (2D) monolayers – adherent to the plastic surface of the vessel in which they are grown. Despite its importance in the early stages of exploratory testing, 2D cell culture does not recapitulate the complex tissue architecture of *in vivo* systems and can fail to model the true infection cycle of a pathogen.

Three-dimensional (3D) cell culture models – which can include multiple cell types, extracellular matrix components and some microfluidic systems – have improved the therapeutic predictions of *in vitro* models with significant advantages to vaccine development. Bioprinting – the process of additively manufacturing biological structures composed of cells and extracellular matrix – now offers cell culture standardization with unprecedented accuracy and reproducibility. Through 3D bioprinting, complex multicellular structures can be created *in vitro* via the layer-by-layer addition of biological materials. Compared to 2D models, these 3D cultures can achieve more accurate responses regarding cell morphology, proliferation capacity and gene expression. They can also offer superior reproducibility and standardization with computer-aided design (CAD).

Cell culture methods are instrumental in the exploratory, testing and production aspects of vaccine development.

"One of the major advantages [of 3D bioprinting] is its reproducibility," says Dr. Stephanie Willerth, associate professor of mechanical engineering at the Center for Biomedical Research, University of Victoria (Canada). Dr. Willerth forged a career in the field of stem cell bioengineering and 3D cell culture innovation.

"The same CAD file can be used with bioprinters all over the world to generate the same structures, provided they have access to appropriate cells and bio-inks," adds Willerth. "Thus, an established tissue model could serve as a benchmark for screening potential vaccines or producing them."

OPTIMAL MEDIA FOR AN OPTIMAL VACCINE

Whether maintained as 2D or 3D structures, cells in culture must be supplied with an appropriate liquid growth medium. Cell culture media – usually a red or pink liquid in which *in vitro* cultures are submerged – is a cocktail of nutrients designed to support and maximize the growth of cells outside of their natural environment.

"The major expenses with 2D cell culture include the media and the labor required to produce the cells and resulting structures," Willerth explains. "Thus, making media formulations that last longer and, in turn, reduce the amount of labor needed to generate a large number of cells is key."

Cell culture media typically includes amino acids, vitamins, salts, sugars and supplementary nutrients. Animal serum is also sometimes added to provide supplemental growth factors and hormones within a tissue environment.

While widely used in cell culture practice, animal serums are often poorly characterized or standardized, if at all. Studies have revealed almost 1,800

proteins and 4,000 metabolites in a routinely used animal serum, with each causing potential variability in *in vitro* experiments. The removal of animal serum from the vaccine production pipeline has been an essential step in accelerating the delivery of therapeutics to market, speeding up exploratory testing and minimizing the number of safety checks needed for each candidate drug.

The supplementation of basal synthetic media – such as MEM, EMEM or DMEM – with additional lab-derived proteinaceous components and metabolites, now supports the scalability and reproducibility requirements for vaccine production. However, the optimization of cell culture media remains an ongoing process, as researchers continue to strive to mimic the complexity of each true tissue microenvironment.

REPLACEMENT, REDUCTION AND REFINEMENT

Animal products have played an essential part in the vaccine production pipeline for many years. However, with increasing public awareness of animal welfare and the scientific risks associated with animal product contaminants, alternative methods of cell-based production remain a priority for vaccine development.

Many human vaccines have been produced successfully and safely in animal cells. Vero cells – an immortalized cell line isolated from the kidney epithelium of the African green monkey – have been widely used in vaccine production, proving instrumental in the fight against SARS-CoV-2.

Many researchers argue that Vero cells do not offer the biological relevance for effective human vaccine development. However, human alternatives are also not without their controversies. In 2021, Johnson & Johnson (Janssen) faced skepticism for allegedly using human fetal cell lines in the production of their SARS-CoV-2 vaccine. While the cells used in the company's pipeline were lab-derived and did not contain any fetal tissue, the public perception of human cell culture has caused some to refuse this vaccine preparation based on its cell-based production methods.

GOING CELL FREE

Messenger ribonucleic acid (mRNA) vaccines now represent a substantial portion of the global therapeutic market, promising to make the production process for vaccines faster still. The market share of mRNA vaccines is expected to reach a value of $15.49 billion within the next five years, raising questions about the future of cell culture in mass vaccine production.

Cell culture media typically includes amino acids, vitamins, salts, sugars and supplementary nutrients.

In vitro synthesis methods for mRNA vaccine production can now bypass cells entirely, creating large volumes of therapeutic grade mRNA within bioreactor systems in a matter of hours. While the potential of this approach has been recognized for some time, developments in mRNA delivery systems have only recently made cell-free vaccines a possibility. According to some experts, mRNA vaccine technology may replace cell-based production methods sooner than we may think.

Dr. Namit Chaudhary is a doctoral candidate at Carnegie Mellon University (Pittsburgh), working on the development of lipid nanoparticles (LNPs) to deliver RNA-based, cell-free therapeutics. "RNA-based vaccines against infectious diseases, such as HIV, influenza, RSV, CMV etc., have already entered clinical trials. If they show positive results, we might have vaccines against several deadly pathogens in the near future," he says. "Both Moderna and Sanofi already have candidates against the flu vaccine in clinical trials. Depending on the results we might have an mRNA-based flu vaccine soon."

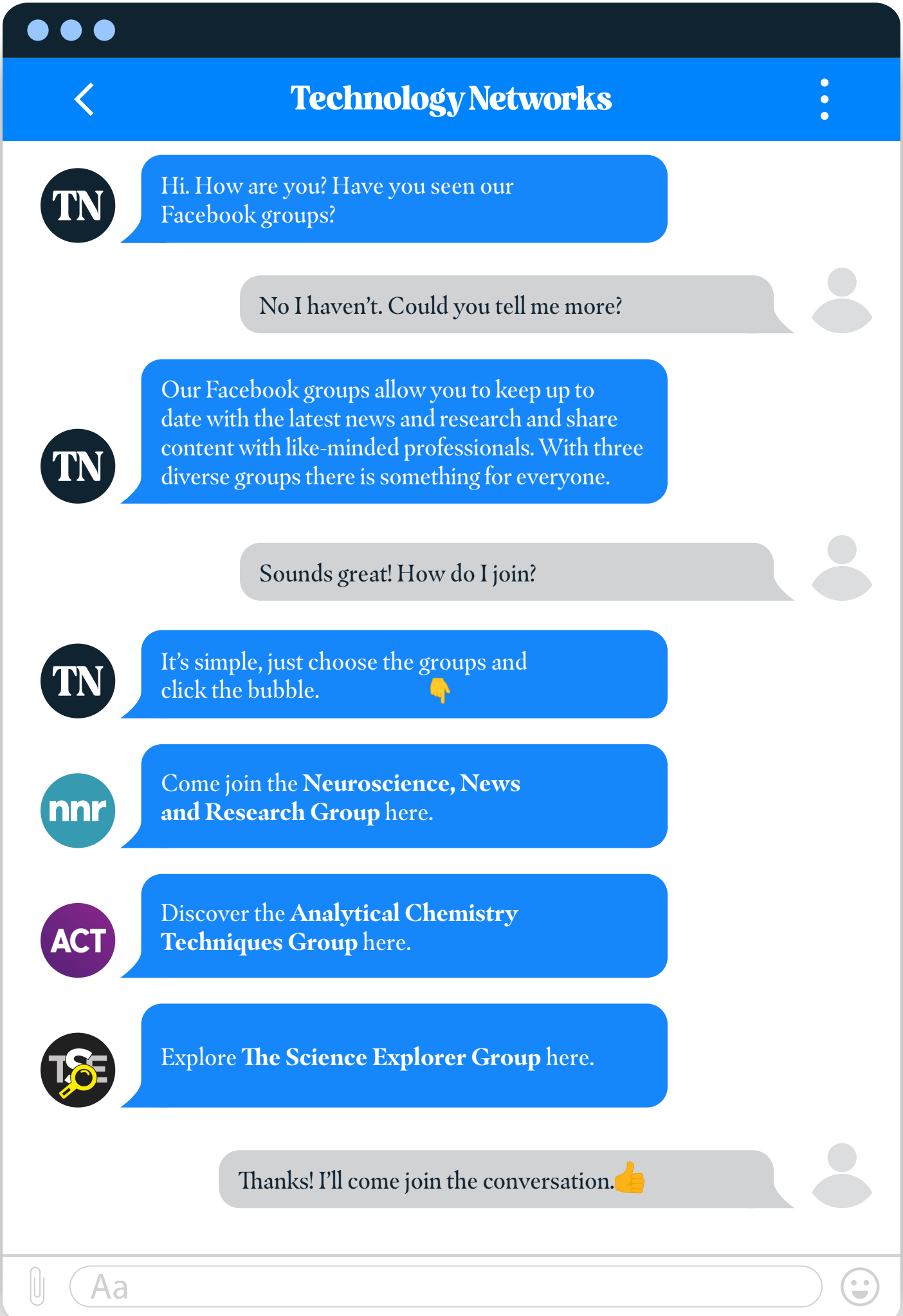
Like bioprinting, mRNA vaccines can come with high relative costs and infrastructure requirements. "One of the key challenges limiting the widespread use of RNA vaccines is their ultra-cold storage requirements," Chaudhary adds. "Thermostable vaccines [like those produced using cell-based methods] that are stable at room temperature for extended periods of time will enable vaccine distribution in low-income countries that don't have ultra-cold supply chains."

CELL-BASED VACCINE PRODUCTION IS HERE TO STAY

While all the licensed COVID-19 vaccines have shown success in clinical trials – and all have been tested using cell culture approaches – there remains room for optimization when it comes to cell-based vaccine production.

The availability of LNP technology for mRNA vaccine production might offer new, cell-free synthesis options, but cells remain necessary for post-production testing. "I think there is still space in the market for all technologies," says Chaudhary. "Cell culture and animal models are still necessary to test the efficacy and immune response of vaccine candidates."

Methods in 3D and serum-free cell culture will likely play an increased role in accurate and reproducible therapeutic testing. However, the high costs associated with lab infrastructure, training and reagents could possibly perpetuate the bio economical privileges of already wealthy nations. Further approaches are required to ensure that technological advancements in vaccine production can translate to global vaccine equity and public health. ●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