GEN Genetic Engineering & Biotechnology News

NOVEMBER 2025

Phage Therapy

Research Spurred by Bird Flu Risk

A-List
Top Drugs
Heading for a Patent Cliff

Synthetic Biology
Embraced by Biopharma

Mass Spectrometry
Sharpens Its Multiomics Focus

AI and Digital Twins
Beyond Process Development

Mary Ann Liebert, Inc. publishers

The power of NGS-based proteomics

Unlock high-throughput proteomic discovery with the new Illumina Protein Prep

By combining SOMAmer® technology with trusted Illumina sequencing and integrated DRAGEN™ secondary analysis, **Illumina Protein Prep** enables you to:

- Detect and quantify **9.5K human proteins** in 2.5 days
- Perform **cost-effective discovery** with the largest NGS-based proteomics panel
- Access **market-leading assay performance** with high sensitivity, specificity, and reproducibility

Experience the new standard in proteomics — all with Illumina.

To learn more, download new eBook.

illumina®

WATCH ON DEMAND

The State of AI in Drug Discovery

Virtual Summit

This summit provides a platform for an outstanding group of researchers, evangelists and entrepreneurs to showcase the latest advances, applications and challenges regarding the deployment of AI across therapeutic development. The program features exciting companies and organizations powering the AI revolution, including NVIDIA, Xaira Therapeutics, Recursion, Chan Zuckerberg Initiative, Arc Institute, Generate:Biomedicines, and more!

FEATURED SPEAKERS

EMMA LUNDBERG

DEREK LOWE

REGINA BARZILAY

BO WANG

STACIE CALAD-THOMSON

WATCH NOW

Watch the dynamic program for free today, featuring:

- A featured presentation with **Bo Wang, PhD** (Xaira Therapeutics) on the promise of multimodal AI for health care
- The democratization of small molecule drug discovery with the developers of Boltz-2, **Gabriele Corso**, **PhD** (MIT), **Regina Barzilay, PhD** (MIT), and **Najat Khan, PhD** (Recursion)
- Evolving industry trends across the AI therapeutic landscape with **Derek Lowe, PhD** (Novartis and author of *In the Pipeline*), **Molly Gibson, PhD**, (Flagship Pioneering), and **Stacie Calad-Thomson, PhD** (NVIDIA)
- Building the virtual cell with **Theofanis Karaletsos** (Chan Zuckerberg Initiative), **Emma Lundberg, PhD** (Stanford), **Hani Goodarzi, PhD** (Arc Institute), and **Ron Alfa, MD, PhD** (Noetik)
- What's next for AI in protein design with **Surge Biswas, PhD** (Nabla Bio), **Tharindi Hapuarachchi, PhD** (Generate:Biomedicines), and **Oliver Vince, PhD** (Basecamp Research)
- Breakout sessions from our event sponsors, Revvity Signals, Benchling, and Telesis Bio

Learn more and discover the full agenda today!
Not able to attend live? No problem! Register to get the on-demand recording.

SCAN TO WATCH FOR FREE

HOSTED BY

GEN Genetic Engineering & Biotechnology News

SPONSORED BY

Benchling TelesisBio revvity signals

GMP Production When and Where You Need It

Drug Substance Manufacturing

- Bioreactor capacity of over 500,000 L
- Single-use, disposable bioreactors
- Scale-out manufacturing model
- Fed-batch or continuous cell culture

Drug Product Manufacturing

- Fully automated, robotic, and gloveless isolator
- Ready-to-use containers and closures
- Liquid and lyophilized vial, prefilled syringe, and autoinjector options
- Autoinjector assembly and clinical supply service

Quality. Expertise. Performance. Capacity.

We operate 16 state-of-the-art GMP drug substance facilities and 9 drug product facilities worldwide. Count on high-quality drug substance and drug product when you need it, where you need it.

Connect with Us

The world's leading global single-source platform from concept to commercialization

wuxibiologics.com

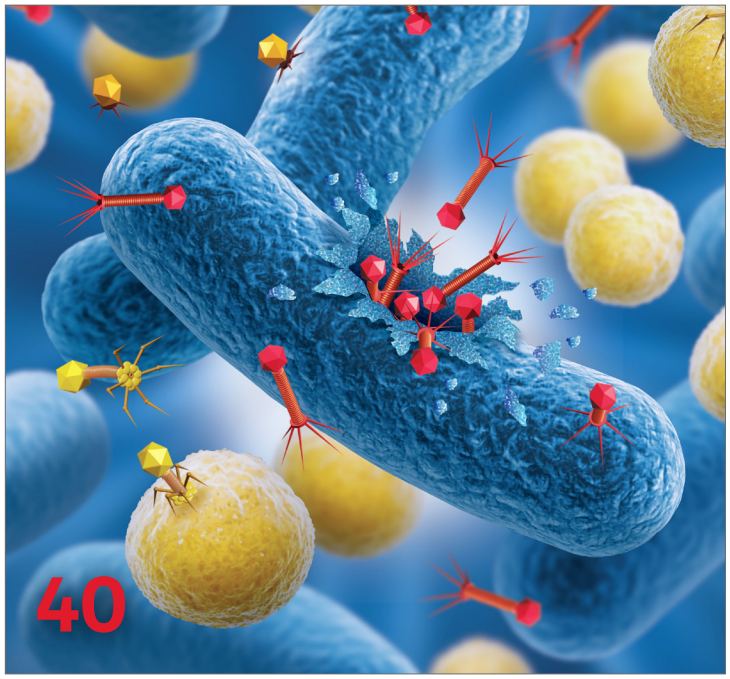
WuXi Biologics
Global Solution Provider

Contents

NOVEMBER 2025 • Vol 45 • Number 11

GEN Genetic Engineering & Biotechnology News

Cover Story INFECTIOUS DISEASE



Bird Flu's Human Risk Spurs Phage Therapy Research

Engineering bacteriophages as precision treatments and vaccine vectors.

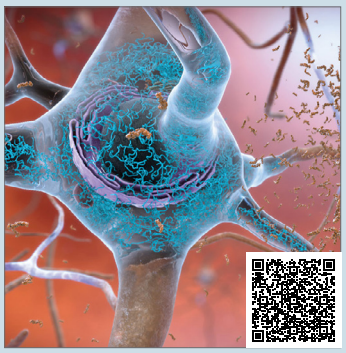
A-LIST

DRUG DISCOVERY

What's **Trending Online** GENengnews.com

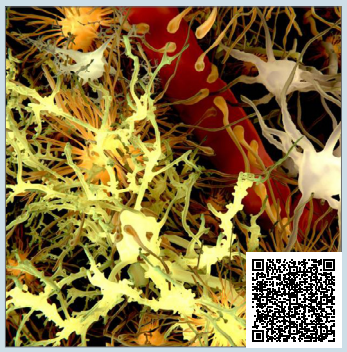
Insilico Medicine

Insilico's AI Workflow Has Two Jobs: Discover Compounds, Thwart Competitors



National Institute on Aging/National Institutes of Health

Nanoparticle Therapy Promotes Aβ Clearance and Cognitive Recovery in Alzheimer's Mouse Model



selvanegra / Getty Images

Astrocyte Activity Linked to How Long-Term Memories Are Formed in Mice

Kevin Davies

Altos Labs Founder Targets "Mesenchymal Drift" to Fight Aging

Cover Image: Multiple companies are advancing phage therapeutics as versatile tools for combating resistant bacterial strains and for developing effective, scalable vaccines against viral diseases. [Armata Pharmaceuticals]

Contents

GEN Genetic Engineering & Biotechnology News

Breaking Bottlenecks in Antibody Discovery

How Gibson SOLA® accelerates the design–build–test cycle

Despite today's biological sophistication behind antibody discovery, many bottlenecks remain. According to Paul DiGregorio, PhD, head of commercial strategy and partnerships at Telesis Bio, the barriers that slow antibody programs today lie not only in computational design or screening capacity, but in the physical act of acquiring DNA to power those screens.

"Balancing throughput versus turnaround time remains one of the major challenges," DiGregorio explains. In conventional antibody-discovery pipelines, researchers rely heavily on third-party gene synthesis services to generate the DNA constructs needed for each iteration of the design–build–test cycle. This dependency introduces delays, variable quality, and uncertainty in delivery timelines—all of which compound to reduce productivity.

Because outsourced synthesis can take a week or more per iteration, each design cycle incurs idle time that stalls screening and analysis. "Researchers are consistently dealing with variable delivery timelines, partial order fulfillment, and variable quality," DiGregorio says. "Each of these factors impacts execution and creates delays that limit how quickly a project can move forward."

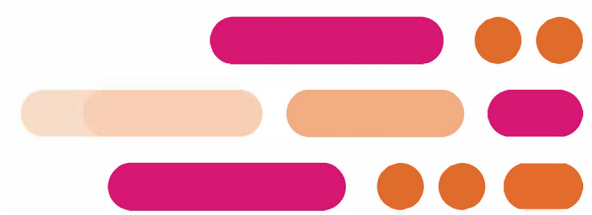
Another inefficiency stems from the synthesis approach employed by many service providers. Antibody sequences share extensive conserved regions across their heavy and light chains, yet service providers must resynthesize entire constructs for every variant. "In reality, researchers are often only modifying a small hypervariable CDR or complementarity-determining region," DiGregorio notes. "Synthesizing whole chains every time wastes time and budget."

Finally, screening itself poses intrinsic constraints. Identifying and refining a lead antibody often requires up to six iterative cycles. Any disruption in the build phase directly impacts the overall discovery timeline.

Bringing synthesis in-house

To address these bottlenecks, Telesis Bio developed Gibson SOLA, an on-demand, enzymatic DNA synthesis platform that enables researchers to synthesize DNA directly in their labs. "Instead of outsourcing synthesis, customers can design and build DNA in-house using stock reagents," says David Weiss, director at Telesis Bio. "These universal reagents work for any sequence, so a lab can go from digital design to having the physical DNA molecule in a day."

SOLA leverages the foundational chemistry of the Gibson assembly, invented by Telesis Bio co-founder Dan Gibson, PhD. The platform



employs a modular, block-based assembly method that Weiss describes as akin to "building DNA from LEGO bricks." Because the reagents are universal, no custom oligonucleotide synthesis is required—reducing both cost and dependency on external suppliers.

What differentiates SOLA from other synthesis solutions is its intelligent synthesis capability, notes Weiss. The Gibson SOLA platform recognizes and reuses conserved DNA sequences across multiple constructs, synthesizing these shared regions only once. The platform then assembles variable regions—such as CDR loops—around these conserved backbones.

"This approach dramatically reduces redundant synthesis," DiGregorio says. "You're only building new DNA for the small hypervariable regions you're testing." The result is lower cost per construct and the ability to evaluate a broader design space. In one benchmark experiment, Telesis Bio screened 200 single-chain, variable fragments. Using SOLA, 93% of heavy and 85% of light sequences were identified as conserved. By synthesizing those regions once and reusing them, synthesis costs dropped by over 50%—while simultaneously enabling a 50% increase in the number of variants screened.

Redefining the pace of antibody discovery

SOLA integrates with standard laboratory automation systems, allowing seamless execution of high-throughput synthesis workflows. The accompanying software generates automated build instructions and supports integration with AI-driven antibody-design pipelines. "The modularity of SOLA really enables machine-learning-guided exploration," DiGregorio says. "It gives researchers the ability to rapidly test AI-generated hypotheses in the wet lab."

As DiGregorio summarizes, "Gibson SOLA enables scientists to focus on what really matters: exploring sequence diversity, understanding binding function, and advancing therapeutic candidates—without being constrained by the slowest step in the process." ■

From the Editor in Chief

"AI can accelerate discovery—or disaster."

— *Science* EDITORIAL, 2024

John Sterling

A recent National Public Radio segment, entitled "AI designs for dangerous DNA can slip past biosecurity measures, study shows," pointed out that many biocompanies that sell custom DNA have long used screening systems to block orders for dangerous genetic material such as smallpox or anthrax. But the NPR reporter also noted a new study published in *Science*[1] demonstrating that AI can now help bypass those safeguards.

The authors show that AI-powered protein design tools can "paraphrase" DNA sequences of toxic proteins, rewriting them so they maintain their harmful function while evading detection. In the study, AI generated over 75,000 variants of hazardous proteins, many of which slipped past the biosecurity filters used by DNA manufacturers around the globe.

Although the screening software was quickly updated, it still failed to catch some reformulated sequences, revealing persistent vulnerabilities. The incident highlights growing fears that AI could accelerate the misuse of biotechnology, allowing the creation of novel biothreats.

To mitigate risks, the researchers and the journal limited access to the study's data and software, with oversight from the International Biosecurity and Biosafety Initiative for Science. This marked the first time such a control model has been used for a scientific publication.

"AI-powered protein design is one of the most exciting frontiers in science. We're already seeing advances in medicine and public health," Eric Horvitz, MD, PhD, CSO at Microsoft told NPR. "Yet like many powerful technologies, these same tools can often be misused."

In addition to the creation of pathogenic organisms, other risks include unregulated labs that could order or synthesize harmful gene sequences for bioterrorism or illicit experimentation if screening procedures are weak. Also, synthetic genes introduced into the environment could spread uncontrollably, potentially wiping out species or altering ecosystems in unpredictable ways or transfer to natural microbes or plants, possibly creating antibiotic resistance or new metabolic pathways that affect ecosystems or human health. Engineered organisms could also produce harmful metabolites or destabilize food chains. Complicating these matters is the increasing accessibility of DIY biology labs and gene printers and rapid technology evolution.

Some potential safeguards are mandating and harmonizing sequence screening worldwide, establishing digital traceability and encryption for all DNA orders, modernizing international treaties like the Biological Weapons Convention with enforcement powers. Integrating cybersecurity and AI oversight into biosecurity, and promoting education, safe-by-design engineering, and international cooperation will be critical.

Despite updated safety protocols, it's hard not to imagine someone with ill intent creating a dangerous biobug. Then the issue becomes one of biocontainment, an incredibly difficult exercise to say the least. In any case, constant, unremitting surveillance combined with readiness for a centralized global response should be planned and implemented in the immediate future.

1. Wittman BJ, Alexanian T, Bartling C, et al. Strengthening nucleic acid biosecurity screening against generative protein design tools. *Science*. 2025;390(6768):82-87.

JSterling@
GENengnews.com

GEN Genetic Engineering & Biotechnology News

Genetic Engineering & Biotechnology News
140 Huguenot Street, New Rochelle, NY 10801-5215
914 740-2100 • GENengnews.com

Genetic Engineering & Biotechnology News (ISSN-1935-472X) is published monthly (twelve issues a year) by GEN Publishing, 140 Huguenot Street, 3rd Floor, New Rochelle, NY 10801-5215. Periodicals postage paid at New Rochelle, NY and at additional mailing offices. Postmaster: Send address changes to *Genetic Engineering & Biotechnology News*, c/o Subscription Department, Mary Ann Liebert, Inc., 140 Huguenot Street, 3rd Floor, New Rochelle, New York 10801-5215. Fax: 914 740-2201. Mailed in Canada under CPC CPM #40026674. Printed in the U.S.A.

For subscription information go to: **www.GENengnews.com/subscription-center**

Mary Ann Liebert, Inc.
a Sage Company

Sticky ends

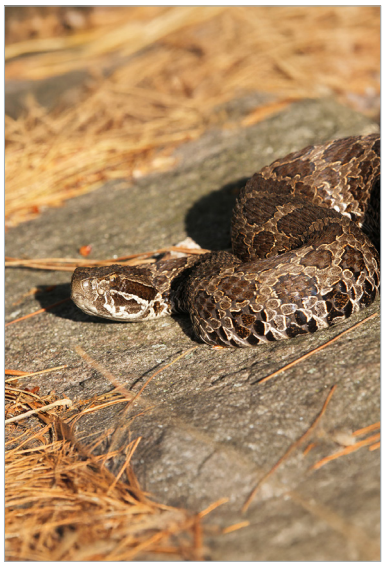
Yogurt Gets an Ant-iquated Twist

David Zilber

Yogurt production was industrialized about a century ago, and today's versions typically rely on just two bacterial strains. But dairy fermentation has been practiced for thousands of years, shaped and refined by diverse regional cuisines. Now, in a new study reported in *iScience*, researchers recreated a nearly forgotten yogurt recipe that was once common across the Balkans and Turkey—using ants. The work showed that bacteria, acids, and enzymes in ants can kickstart the fermentation process. More specifically, the acids from the lactic and acetic acid bacteria carried by the ants help coagulate the dairy. In addition, formic acid, which is part of the ant's natural chemical defense system, acidifies the milk, affects its texture, and likely creates an environment for yogurt's acid-loving microbes to thrive. To test out the contemporary culinary possibilities of ant yogurt, the team partnered with chefs at Alchemist, a two Michelin Star restaurant in Copenhagen, Denmark, who gave the traditional yogurt a modern twist. They served guests yogurt ice-cream sandwiches shaped like an ant, mascarpone-like cheeses with a pungent tang, and cocktails clarified with a milk wash—all inspired by ant yogurt and using the insect as a key ingredient.

Snakes Choose the Snake Next Door

Rattlesnakes may not be the most beloved animals, but they play a vital role in their ecosystems. As keystone species in wetland food webs, they help maintain ecological balance by preying on rodents like mice and rats. The Eastern Massasaugas of Michigan don't typically like to venture beyond the wetland where they were born; they wander only to find a mate before returning home. But increasing human presence—and developments such as roads, farms, and houses—are keeping the snakes more homebound. So, when it's time to choose a mate, they are more likely to end up with a relative. Now, a study published in *Proceedings of the National Academy of Sciences* shows that fragmentation of the rattlesnakes into smaller, more isolated patches is likely reducing the threatened snake's chances of survival. They found that the most inbred snakes were 13% less likely to have surviving offspring and had a nearly 12% lower annual survival rate. "These are fairly large and stable populations of Eastern Massasaugas," said Sarah Fitzpatrick, PhD, MSU professor. "The fact that we're detecting problems from inbreeding in these populations is concerning, given that many other populations throughout the Midwest are much smaller and even more fragmented."



khorner / iStock / Getty Images Plus

Claudia Fugazza

Good Dog! Canines Categorize Toys

Fetching a ball, or tugging on a rope, may seem like simple-minded tasks for a dog. But a new study in *Current Biology* suggests that there may be more going on in a dog's mind than previously thought. The research describes how dogs can categorize objects by function; they can infer how similar types of toys work, even when the toys don't look alike. In a series of playful interactions with their owners, a group of Gifted Word Learner (GWL) dogs were able to distinguish between toys used for tugging versus fetching, even when the toys in question didn't share any obvious physical similarities—and then could remember those categorizations for long periods of time, all with no prior training. "We discovered that these Gifted Word Learner dogs can extend labels to items that have the same function or that are used in the same way," says Claudia Fugazza, PhD, of Eötvös Loránd University, Budapest, Hungary. It's like a person calling both a traditional hammer and a rock by the same name, says Fugazza. "The rock and the hammer look physically different, but they can be used for the same function," she says. "It turns out that these dogs can do the same."

Largest Genetic Map of Human Metabolism Created

vatrushka67 / iStock / Getty Images Plus

The contribution of genetics to the variability in people's metabolism has remained largely unknown. This is, in part, because genetic studies of human metabolism have been limited in scale and allelic breadth. Now, the largest genetic map of human metabolism has been created, revealing new insights on the role of metabolites in health and disease and creating a blueprint for further research.

This work is published in *Nature Genetics* in the paper, "A genetic map of human metabolism across the allele frequency spectrum."

The team used UK Biobank data from ~450,000 individuals of European, African, and Asian ancestry living in the U.K. The authors examined the consequences of variation in the human genetic code on blood levels of 249 small molecules including lipid levels.

More specifically, the group presents a map of the genetic regulation of circulating small molecules and lipoprotein characteristics (249 traits) measured using proton nuclear magnetic resonance spectroscopy across the allele frequency spectrum. Trans-ancestral meta-analyses identified 29, 824 locus–metabolite associations mapping to 753 regions.

Combined with genetic data, the researchers found that genetic control of metabolites was very similar across ancestries and between men and women and large ancestral groups represented in UK Biobank. This included genes with previously unknown roles in metabolism.

The study also provided insights into genes associated with metabolism that predispose to disease. In addition, they "observe and classify extreme genetic pleiotropy, identify regulators of lipid metabolism, and assign effector genes at >100 loci through rare-to-common allelic series."

Lastly, they propose roles for genes less established in metabolic control (for example, *SIDT2*), genes characterized by phenotypic heterogeneity (for example, *APOA1*) and genes with specific disease relevance (for example, *VEGFA*).

Studies of this magnitude are made possible by the emergence of biobanks worldwide. "We are now able to map systematically the genetic control of hundreds of blood molecules, at unprecedented scale," said Martijn Zoodsma, PhD, postdoctoral researcher at the BIH in Berlin. "This provides a powerful reference to understand disease risk and identify genes that contribute to variability in metabolism."

"The development of blood lipid-lowering medications, such as statins, has saved numerous lives, but heart diseases remain the major killer," noted Maik Pietzner, PhD, professor for Health Data Modelling at BIH and Queen Mary's Precision Health University Research Institute (PHURI). "Our results highlight potential avenues that will hopefully lead to new medicines to prevent even more deaths from lipid plaques building in people's arteries." GEN

THE STATE OF BIOTECH
VIRTUAL SUMMIT

WATCH NOW ON DEMAND


GEORGE CHURCH, PHD

Watch the *Genetic Engineering & Biotechnology News'* flagship virtual event, The State of Biotech! Discover how distinguished researchers and business leaders from the industry are reshaping biotech.

Featuring a Keynote Presentation from George Church, PhD, of Harvard Medical School


IYA KHALIL, PHD


DAPHNE ZOHAR

Hear additional exciting speakers including:

- **Iya Khalil, PhD** (Merck & Co.)
- The co-hosts of the popular *Biotech Hangout* podcast—**Daphne Zohar**, **Brad Loncar**, and **Chris Garabedian**
- **Rodolphe Barrangou, PhD** (NCSU); **Geulah Livshits, PhD** (Chardan); and **Amber Salzman, PhD** (Epicrispr)
- **Aiken Hackett** (BIO) and **Yvette R. Seger, PhD** (FASEB)


BRAD LONCAR


CHRIS GARABEDIAN


RODOLPHE BARRANGOU, PHD


GEULAH LIVSHITS, PHD


AMBER SALZMAN, PHD

Watch Now On Demand For FREE

Hosted by

GEN Genetic Engineering & Biotechnology News

Sponsored by

cytiva

Could ALS Be an **Autoimmune Disease?**

Dr_Microbe / iStock / Getty Images Plus

Researchers have uncovered evidence that amyotrophic lateral sclerosis (ALS) may be an autoimmune disease. The team discovered that inflammatory CD4+ T cells mistakenly target certain proteins that are part of the nervous system in people with ALS. A paper describing their work, "Autoimmune response to C9orf72 protein in amyotrophic lateral sclerosis," appears in *Nature*.

"This is the first study to clearly demonstrate that in people with ALS, there is an autoimmune reaction that targets specific proteins associated with the disease," says La Jolla Institute for Immunology Professor Alessandro Sette, PhD, who co-led the study with Professor David Sulzer, PhD, of the Columbia University Irving Medical Center.

The scientists found that people with ALS produce high numbers of CD4+ T cells that target the C9orf72 protein, which is expressed in neurons. This kind of "self-attack" is the defining feature of autoimmune disease.

"There is an autoimmune component to ALS, and this study gives us clues as to why the disease progresses so rapidly," says Sulzer. "This research also gives us a possible direction for disease treatment."

Around 5,000 Americans are diagnosed with amyotrophic lateral sclerosis (ALS) each year. About half of patients die within 14 to 18 months of being diagnosed, usually due to breathing failure. The exact cause of ALS has long been unknown.

Two patient groups with different survival times

Although ALS usually progresses quickly, around ten percent of patients live with the disease for ten years or longer. Baseball player Lou Gehrig passed away just two years after his ALS diagnosis. In contrast, physicist Stephen Hawking, PhD, lived for 55 years following his diagnosis.

Scientists aren't sure what accounts for this variation. Researchers have linked certain genetic and environmental factors to different ALS "subtypes," but don't have a broad explanation to account for different survival times in most patients.

The new study suggests the immune system plays a big role in patient survival times. By examining T-cell responses in ALS patients, the researchers were surprised to find two distinct patient groups. One group had shorter predicted survival times. Their inflammatory CD4+ T cells were quick to release inflammatory mediators when they recognized C9orf72 proteins.

The second patient group also had harmful inflammatory CD4+ T cells, but they also had higher numbers of different T cells, anti-inflammatory CD4+ T cells. This second group also had significantly longer projected survival times.

Anti-inflammatory CD4+ T cells are important because they can regulate disease. When the immune system fights a viral infection, for example, it churns out inflammatory T cells to eliminate the infected cells. Once the immune system clears the virus, anti-inflammatory CD4+ T cells step in to prevent overzealous T cells from damaging healthy tissues.

The scientists weren't expecting to observe this same process in ALS patients. The new research suggests that CD4+ T cells may reduce harmful autoimmune responses and slow the progression of ALS.

"This protective T-cell response is strongest in people with a longer predicted survival time," says Emil Johansson, PhD, a visiting scientist in the Sette Lab.

Next steps in ALS research

Future ALS therapies might boost protective CD4+ T-cell responses and dial back harmful inflammation, says LJI research technician Tanner Michaelis, who served as the study's first author.

"Hopefully, now that we know the specific target for these immune cells, we can make more effective therapies for ALS," says Michaelis.

"There are several neurodegenerative diseases where we now have clear evidence of immune cell involvement," explains Sette. "This is turning out to be more of a rule of neurodegenerative diseases—rather than an exception." GEN

The Newest New Approach Methodologies

NAMs, from advanced cell models to AI-based predictive studies, are advancing the biopharmaceutical industry

Although new approach methodologies (NAMs) are not that new, they remain a crucial and evolving aspect of the development and production of biopharmaceuticals. "NAMs have been around for 20 years plus," says Julie Frearson, PhD, senior vice president, chief scientific officer at Charles River Laboratories, which is a contract research, development, and manufacturing organization headquartered in Wilmington, MA. "In many ways, NAMs are a hot topic at the moment, because of FDA policy shifts and NIH commentary."

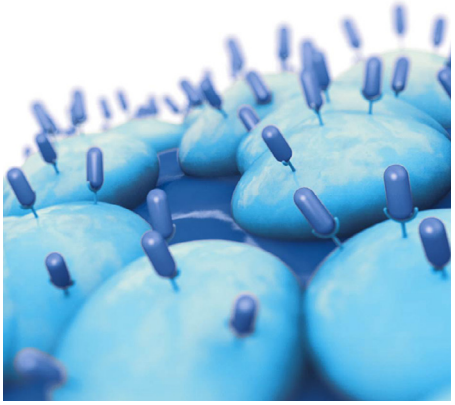
In general, NAMs provide alternatives to the traditional methods that are used to understand a drug or chemical's efficacy or toxicity. These methods include *in vitro* models, such as cell-based assays, and *in silico* models, like mechanistic or AI-based predictive models. "NAMs also cover the concept of downgrading from a large species to a smaller species—for instance, the opportunity to use a transgenic mouse rather than a large-animal model in a given study."

NAMs address two key objectives in the biopharmaceutical industry. One is that NAMs can "increase a pharma company's productivity and their chances of success on a therapeutic program, because using human-based assays can theoretically improve your chances that a drug will be safe and efficacious in humans," Frearson says. "Then, the second paradigm is reducing the animal footprint in discovery and nonclinical development." As she emphasizes, "everybody wants to use fewer animals."

From *in vitro* to AI

NAMs can augment and improve drug-development workflows in many ways across drug discovery and de-risking for safety. "The ability to use these systems has been accelerated by a continued evolution in the sophistication of advanced cell models through bioengineering, iPSC technology, and human cell or tissue supply in general," Frearson says. The AI and computation innovation wave also plays a key role in those improvements, particularly in combination with advanced cell models. For example, using mechanistic modeling, "you can take data from multiple *in vitro* systems to feed a computational model to predict human toxicity," Frearson says. Moreover, Charles River is using AI and machine learning in drug design.[1] "It's helping us to rapidly assess whether or not a given structure will do the right things *in vivo*: predicting that in the computer, rather than having to run the experiments," Frearson says.

In continued attempts to reduce its animal footprint, Charles River scientists have also combined decades of datasets to develop virtual control groups.[2] "That enables us to think about future studies, where we don't need a real control arm," Frearson says. Furthermore, Charles River's Retrogenix®[3] microarray platform provides a totally animal-free method of testing if a drug binds its target and the level of nonspecific binding, which Frearson calls "the earliest indicator of whether you're going to have a safety problem." This *in vitro* platform was recently accepted into the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program, which is the first step towards being considered for regulatory approval.



AI-enhanced visualization of cellular receptor landscapes: a conceptual rendering illustrating the potential of New Approach Methodologies to decode complex biological interactions without animal testing. [Custom illustration | Charles River]

In the future, NAMs will be used in many biopharma processes moving beyond discovery and non-clinical development and into testing of pharmaceutical products before release. "More of today's *in vivo* assays could become *in vitro*, and *in silico*, and combinations thereof," Frearson says. "For the medium term, we are viewing NAMs as largely augmenting *in vivo* studies resulting in refinement and reduction of animal use and safer, more effective therapeutics." ■

References available online.

Targeting the Tumor Microenvironment: A Promising New Approach

By Gail Dutton

Targeting functional proteins within the TME may eradicate the entire tumor in multiple cancer types

Existing oncology therapeutics are either so specific they can target only part of a tumor, or so generalized they kill healthy tissue.

A new "Tumor Activated Therapy™" in development at the small virtual company Seekyo Therapeutics seeks to target only the functional proteins that are always present in all solid tumors. Although still at the preclinical stage (including animal testing), this early work suggests it may be efficacious, relatively low-cost, and safe for multiple types of solid tumors. If those results hold true in further preclinical and eventual clinical studies, Tumor Activated Therapy may have the potential to become a breakthrough cancer therapeutic.

Targeting functional proteins

"In solid tumors, there are many kinds of different cancerous cells. We needed a strategy that would affect all types of cancerous cells at the same time," Oury Chetboun, Seekyo's CEO and co-founder, tells *GEN*.

To do that, Chetboun explains, Sébastien Papot, PhD, professor at the University of Poitiers and the French National Center for Scientific Research (CNRS), and Seekyo's co-founder and chief scientific officer, developed a method that encompasses "the functional proteins present in the tumor microenvironment [TME] to destroy all the different cancer cells inside the same tumor."

The company's lead compound, SKY01, links to albumin in the patient's blood stream and becomes a macromolecule. It uses the pharmacokinetics of albumin—which the tumor sees as a nutritional source—to draw the macromolecule to the tumor, and the beta glucuronidase within the TME to release monomethyl auristatin E, a cytotoxic payload that induces apoptosis. "Therefore, we don't need to get inside the cell to be active," Chetboun points out. "We just need to be inside the TME."

In contrast, he says, "Antibody drug conjugates (ADCs) target a specific marker on the surface of tumor cells." They must be transported inside the cells in order to destroy the cancer. ADC's downside is that it targets only cells expressing specific markers, leaving other cancerous cells intact, which limits the effectiveness of the therapeutic.

At first glance, one may wonder if Seekyo's Tumor Activated Therapy could eradicate tumors even before they are detected. That assumption would be erroneous, Chetboun says. "If a tumor hasn't been detected, beta-glucuronidase isn't accumulating and SKY01 can't be activated," he explains.

Although present in low concentrations inside healthy cells (specifically, the lysosome), "Beta-glucuronidase appears to be produced and accumulated at high concentration only at the tumor site," Chetboun elaborates. Because SKY01 can't penetrate the cell, it only encounters that enzyme in the tumor microenvironment.

The release mechanism is like an on/off switch, he emphasizes. "Either you have the enzyme (in the TME) and the payload is released, or you don't have the enzyme (in the TME) and it can't be released. That brings a high level of selectivity and safety for the patient…that could prevent any off-target activation."

An earlier-stage program, SKY02, uses the same mechanism to deliver an immune system stimulant to tumors. He speculates that it may be possible eventually to administer SKY01 and SKY02 as a potent combination therapy.

"Patients, cancers, and stages are different from one another, so oncologists need several tools in their toolbox to win," Chethboun points out.

The mechanism of action Chetboun describes is considerably simpler than those of most gene or immunotherapies. For example, unlike with CAR T therapies, "You don't need to extract a patient's blood, modify cells, and reinject them,"

Vital SIGNS

Seekyo Therapeutics

Location
Chasseneuil-du-Poitou, France

Website
seekyo-therapeutics.com

Principal
Oury Chetboun
Co-founder and CEO

oury.chetboun@seekyo-therapeutics.com

Number of Employees
1–5

Focus
A preclinical biopharmaceutical company developing a "Tumor Activated Therapy™" to target the tumor microenvironment.

he points out. This simplicity may enable this therapeutic to overtake more advanced programs in terms of commercialization.

In terms of production, the product is lyophilized and reconstituted just before it is administered. This offers a potentially long shelf-life without the need for cold storage, which could eventually help lower costs, not only for production, but also for the hospital and patient.

Early results

Seekyo proved its concept using patient-derived xenografts implanted into humanized mice. Compared to the standard of care—gemcitabine and nab-paclitaxel—SKY01 dramatically shrank tumor volumes within only a few days. "That's true for pancreatic, triple-negative breast, lung, and colorectal cancers," he says, "and data is coming in now for glioblastoma cancer."

Chetboun also cited data from an experiment in pancreatic cancer in which the cancerous cells were located in the head of the pancreas. After injecting SKY01 at one end of the pancreas, histopathology showed the cancer was eradicated. Then, when examining the body of the pancreas, "We saw no lesions," Chetboun reports. "There was no accumulation of monomethyl auristatin E… no activation inside anything else, even in such a small organ."

When it's time to begin clinical trials, he says an umbrella trial may be possible, involving about 40 patients who have a mix of indications: pancreatic, triple-negative breast, lung, and colorectal cancers. Efficacy in that trial will dictate the focus of subsequent trials.

Now the goal is to lengthen the time between administrations beyond two to three weeks.

The company also is working on diagnostic tools to help monitor SKY efficacy. One approach involves the induced volatolomics technology developed by Papot to detect volatile cancer markers, such as those in the blood. "There's a correlation between the concentration of those markers and the tumor size," Chetboun says. Initial applications will be for patient stratification and, later, to inform personalized therapy.

CNRS collaboration

Seekyo Therapeutics was founded in 2018 based on two decades of drug targeting work by Papot.

The company has maintained a lean structure aimed at maximizing every Euro raised. Research, for example, is still contracted out to CNRS. Whatever it can't do will be performed by a CRO or CDMO.

With this virtual company structure, Seekyo has worked with multiple biotech and big pharma companies to help optimize or widen the therapeutic window of drugs that those organizations are developing. "That shows the technology works and that we can manage such specific relationships," he says.

Next steps

For this work to advance to human trials, Seekyo will need to produce GMP-grade product and increase the number of preclinical test subjects. "And that requires funding," Chetboun stresses.

The company has raised some €2.5 million in financing from angel investors and the French Public Bank of Investment (Bpifrance) in the past seven years. Now Chetboun is looking further afield, searching out opportunities for strategic partnerships and other investments.

At the same time, he's working to identify a top-quality CRO or CDMO. "For the next several years," he says, "everything has to be outsourced, so we need to find the right partners." That includes adding board members with expertise in translational medicine. "It's a challenge to find the right people."

At this early stage, Tumor Activated Therapy appears promising, but even if it scales perfectly, Chetboun cautions, "There will never be one drug for all cancers. There will always be a need for several therapeutic options." GEN

Oury Chetboun in the labs at Seekyo Therapeutics.

How NEB's Customized Solutions Team Drives Innovation and Partnership in Biotech

When developing novel life science products, developers may face challenges in areas such as technical expertise, reagent optimization, manufacturing scale, turnaround time, reagent quality, and comprehensive logistical support. These complexities are particularly magnified within regulated markets. In this Q&A, **John Pezza, PhD**, Customized Solutions Director at New England Biolabs® (NEB®), and **Mike Pelletier**, NEB's Director of Global Operations, discuss the resources and support that companies should expect from a reagents partner to navigate these challenges that come with developing custom products.

Q: What should customers expect from a customized solutions vendor (provider)?

John Pezza, PhD
Customized Solutions Director, New England Biolabs

John: Customers should look for a combination of flexibility, operational integration, quality assurance, and evidence of long-term commitment from their custom solutions vendor. Flexibility requires a technical capability to tailor solutions to a wide variety of needs, ranging from minor formulation adjustments to complex, end-to-end product development. A flexible vendor will also be able to support customers at every stage, from early development and pilot batches to full-scale commercial production, with the agility to scale volume and adapt to evolving requirements.

Additionally, customers should expect the integration of robust, well-coordinated operational systems across manufacturing, testing, packaging, and logistics. Our customized solutions infrastructure was built upon our own internal standards, standards shaped by decades of scientific innovation. This means our customers benefit from the same rigor and reliability we apply to our own product development.

Finally, customers need quality assurance. They should expect a comprehensive, audit-ready package that meets internal quality standards and external regulatory expectations, as well as support from a quality team with extensive experience in regulated markets.

These three pillars are strengthened by our commitment to long-term partnerships and to sustainability, both of which inform how we design, produce, and deliver our products.

New England Biolabs

Q: How can vendors minimize the lead time for custom product development?

John: Lead time is shaped by several key factors, including communication, process integration, and the ability to scale efficiently. At NEB, we emphasize open, frequent, and transparent dialogue—supported by direct access to our scientific staff—to ensure that the development of custom products remains on track and aligned with customer expectations.

Additionally, our vertically integrated model allows us to streamline timelines by reducing handoffs and maintaining control over key steps in the process. Finally, whether a customer is scaling up from R&D or preparing for commercial launch, our flexible infrastructure and collaborative approach help minimize delays and maximize efficiency.

Q: How do vendors ensure they are able to meet current and future needs?

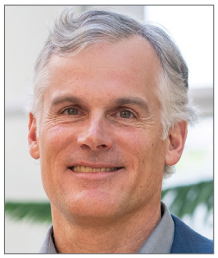
Mike: Meeting current and future needs requires foresight, agility, and a commitment to continuous improvement. As a privately held company, NEB has the flexibility to invest in infrastructure, technology, and people without being constrained by short-term returns.

Unlike vendors who invest reactively, we have the freedom to take a forward-looking approach: anticipating customer needs and investing ahead of demand. For instance, we built a 40,000-square-foot Good Manufacturing Practice-grade (GMP-grade*) production

facility before the pandemic, enabling us to supply critical reagents for vaccine and other therapeutic modalities at scale. In 2023, we expanded our production infrastructure further with the addition of 100,000-square-feet of space, significantly increasing our capacity to support customers across a broader range of applications and volumes. We also opened a 30,000-square-foot lyophilization facility to meet the growing demand for room temperature-stable molecular biology products.

These investments are part of a broader strategy that includes ongoing support for basic research, new product development, and infrastructure expansion, all designed to ensure that we can meet current and future customer needs. In parallel, we continue to invest in sustainable practices across our operations, from energy-efficient facility design to waste reduction initiatives. By staying ahead of the curve, NEB ensures that our customers have access to the capabilities, capacity and innovation they need—not just today, but well into the future.

Q: How can customers vet their custom solutions vendor?



Mike Pelletier
Director, Global Operations
New England Biolabs

Mike: NEB encourages prospective customers to visit our facilities in person. These visits offer a firsthand look at our operations and provide an opportunity to meet the people behind the products. Our team's enthusiasm, expertise, and commitment to customer satisfaction are best experienced face-to-face. Often, facility visits spark new ideas and uncover opportunities that might not emerge through emails or phone conversations alone.

We also encourage customers to schedule audits in advance to ensure the best possible experience, supported by a dedicated audit team. Our facilities and documentation are designed to meet the highest quality standards, and we view audits as an opportunity to build trust, demonstrate transparency, and strengthen long-term partnerships.

Q: What might surprise people about NEB's customized solutions offering team?

John: Many are surprised by the depth and integration of NEB's customized solutions and capabilities. We offer a truly end-to-end experience: from collaborative development and custom formulation to a wide range of fill sizes, container types (including plate filling), and customer-branded packaging. Our dedicated lyophilization facility and in-house oligonucleotide production allow us to support customers with unique supply chain needs, offering a level of control and responsiveness that's rare in the industry. Crucially, these capabilities are not siloed—they're part of a unified, vertically integrated platform designed to deliver scientific and operational value.

The scalability of our operations often exceeds expectations. We have supported pandemic-level demand without interruption—including for key partners such as Moderna—while our documentation has been refined through decades of audits to meet the highest standards across diverse applications. Moreover, our quality team has significant experience in regulated markets, ensuring that customer compliance requirements are properly understood and consistently met.

The depth and scale of our capabilities is enabled by the institutional knowledge of our employees. Our exceptionally low employee turnover ensures continuity and accumulated expertise, and our scientific staff remains engaged throughout the collaboration. Many of the same scientific staff who develop our products are also involved in customization efforts, providing continuity and deep technical insight. This long-term engagement fosters trust, accelerates problem-solving, and ensures that customers receive consistent, high-quality support across the lifecycle of their products. ■

* "GMP Grade" and "GMP-grade" are branding terms NEB uses to describe products manufactured or finished at NEB's Rowley facility. The Rowley facility was designed to manufacture products under more rigorous infrastructure and process controls to achieve more stringent product specifications and customer requirements. Products manufactured at NEB's Rowley facility are manufactured in compliance with ISO 9001 and ISO 13485 quality management system standards. However, at this time, NEB does not manufacture or sell products known as Active Pharmaceutical Ingredients (APIs), nor does NEB manufacture its products in compliance with all of the Current Good Manufacturing Practice regulations.

A-List

Top 20 Drugs Heading for the Patent Cliff, 2026-2029

The White Cliffs of Dover do not seem as daunting as the proverbial patent cliff faced by biopharmas that are about to lose an estimated $230 billion in annual sales as their longtime blockbuster drugs see their patents expire in the coming years. [Immanuel Giel / Wikimedia Commons]

Last year, these treatments accounted for 75% of the $236B in annual sales set to vanish with the loss of exclusivity

By Alex Philippidis

The idea of a "patent cliff" wave of exclusivity expirations shaking up the biopharma industry isn't new: *GEN* first mentions the term in 2010 and again a year later when Lipitor (atorvastatin) lost its basic U.S. patent protection. *The Economist* used the phrase as early as 2009, a year after describing the phenomenon less deftly as a "looming patent-expiry crisis."

However, the proverbial cliff has never loomed as large over biopharma as it will over the remainder of this decade, as key patents are set to expire on billion-dollar-plus "blockbuster" drugs generating approximately $230 billion in annual sales between this year and 2030.

The scramble by biopharmas to recoup the revenues to be lost as blockbusters and less lucrative drugs lose exclusivity helps explain a recent surge of mergers-and-acquisitions activity. The top three deals at deadline:

• **Johnson & Johnson** in April closed this year's largest acquisition at deadline, its $14.6 billion buyout of Intra-Cellular Therapies, a neurological drug developer.

• **Merck & Co.** on October 7 completed its $10 billion purchase of Verona Pharma, a deal designed to expand the pharma giant's pipeline and portfolio of cardio-pulmonary disease treatments.

• **Sanofi** in July closed on its up-to-$9.5 billion acquisition of Blueprint Medicines, a deal intended to expand the buyer's rare immunological disease portfolio.

Shown is *GEN's* first-ever A-List of top 20 blockbusters set to lose the protection of key U.S. patents—five drugs for each year between 2026 and 2029, ranked by their total revenue for the first half of this year and all of 2024 (as furnished by the companies in regulatory filings and/or press releases).

Drugs are grouped by year based on what companies disclosed as the year of expiration for their patent family or key patents, as stated in annual reports also filed with regulators. Each drug is listed by its trade and generic names, the company or companies that market the treatment, the year of initial U.S. approval, and revenue.

GEN's research found that the top 20 drugs heading for the patent cliff accounted for a combined $176.442 billion in sales last year—75% of the $236 billion in annual sales set to disappear with the loss of exclusivity, a combined sales figure widely quoted by biopharma market watchers that includes Deloitte and EY.

Also found were numerous additional drugs whose patents are set to expire between 2026 and 2029:

• **2026**: Merck's Januvia® (sitagliptin; $2.255 billion); Pfizer's Xeljanz® (tofacitinib, $1.618 billion); and Merck's Janumet® and its extended-release version Janumet® XR (sitagliptin and metformin hydrochloride, $1.433 billion).

• **2027**: Pfizer's Ibrance® (palbociclib; $6.393 billion).

• **2028**: Amgen and Pfizer's Enbrel® (etanercept; $5.386 billion).

• **2029**: Amgen's Repatha® (evolocumab; $3.574 billion); Gilead Sciences' Genvoya® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide; $2.503 billion).

2026

> Farxiga® (dapagliflozin)
AstraZeneca
INITIAL U.S. APPROVAL: 2014
REVENUE: $4.209 billion in Q1-Q2 2025; $7.656 billion in 2024

> Prevnar 13/Prevenar 13
(pneumococcal 13-valent conjugate vaccine [diphtheria CRM_{197} Protein])
Pfizer
INITIAL U.S. APPROVAL: 2010
REVENUE: $3.043 billion in Q1-Q2 2025; $6.411 billion in 2024[1]

> Revlimid® (lenalidomide)[2]
Bristol Myers Squibb
INITIAL U.S. APPROVAL: 2005
REVENUE: $1.774 billion in Q1-Q2 2025; $5.773 billion in 2024

> Lenvima® (lenvatinib)
Eisai and **Merck & Co.**
INITIAL U.S. APPROVAL: 2015
REVENUE: $1.606 billion in Q1-Q2 2025 (¥164.3 billion [$1.083 billion] Eisai + $523 million Merck); $2.971 billion in 2024 (¥297.6 billion [$1.961 billion] Eisai + $1.010 billion Merck)[3]

> Bridion® (sugammadex)
Merck & Co.
INITIAL U.S. APPROVAL: 2015
REVENUE: $902 million in Q1-Q2 2025; $1.764 billion in 2024

2027

> Eylea® / Eylea HD® (aflibercept 2 mg / 8 mg)
Regeneron Pharmaceuticals and **Bayer**
INITIAL U.S. APPROVAL: 2011
REVENUE: $4.138 billion in Q1-Q2 2025 ($2.190 billion Regeneron + €1.677 billion [$1.948 billion] Bayer); $13.386 billion in 2024 ($9.545 billion Regeneron + €3.306 billion [$3.841 billion] Bayer)[4]

> Ocrevus® (ocrelizumab)
Genentech, a member of the **Roche Group**
INITIAL U.S. APPROVAL: 2017
REVENUE: CHF 3.506 billion ($4.377 billion) in Q1-Q2 2025; CHF 6.744 billion ($8.419 billion) in 2024

> Xtandi® (enzalutamide)
Astellas Pharma and **Pfizer**
INITIAL U.S. APPROVAL: 2012
REVENUE: $3.877 billion in Q1-Q2 2025 (¥433.3 billion [$2.854 billion] Astellas + $1.023 billion Pfizer); $7.925 billion in 2024 (¥893.6 billion [$5.886 billion] Astellas + $2.039 billion Pfizer)[5]

> Trulicity® (dulaglutide)
Eli Lilly
INITIAL U.S. APPROVAL: 2014
REVENUE: $2.187 billion in Q1-Q2 2025; $5.254 billion in 2024

> Lynparza® (olaparib)
AstraZeneca and **Merck & Co.**
INITIAL U.S. APPROVAL: 2014
REVENUE: $2.246 billion in Q1-Q2 2025 ($1.564 billion AstraZeneca + $682 million Merck); $4.383 billion in 2024 ($3.072 billion AstraZeneca + $1.311 billion Merck)[6]

2028

> Keytruda® (pembrolizumab)[7]
Merck & Co.
INITIAL U.S. APPROVAL: 2014
REVENUE: $15.161 billion in Q1-Q2 2025; $29.482 billion in 2024

> Eliquis® (apixaban)
Bristol Myers Squibb and **Pfizer**
INITIAL U.S. APPROVAL: 2012
REVENUE: $11.171 billion in Q1-Q2 2025 ($7.245 billion BMS + $3.926 billion Pfizer); $20.699 billion in 2024 ($13.333 billion BMS + $7.366 billion Pfizer)

> Opdivo® (nivolumab)
Bristol Myers Squibb
INITIAL U.S. APPROVAL: 2014
REVENUE: $4.824 billion in Q1-Q2 2025; $9.304 billion in 2024

> Gardasil® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] and Gardasil® 9 (Human Papillomavirus 9-valent Vaccine, Recombinant)]
Merck & Co.
INITIAL U.S. APPROVAL: 2006 / 2014
REVENUE: $2.453 billion in Q1-Q2 2025; $8.583 billion in 2024[8]

> Jakafi® / Jakavi® (ruxolitinib)
Incyte / Novartis[9]
INITIAL U.S. APPROVAL: 2011
REVENUE: $2.489 billion in Q1-Q2 2025 ($1.473 Incyte + $1.016 billion Novartis); $4.728 billion in 2024 ($2.792 billion Incyte + $1.936 Novartis)

2029

> Jardiance® (empagliflozin)
Boehringer Ingelheim and **Eli Lilly**
INITIAL U.S. APPROVAL: 2014
REVENUE: $6.693 billion (€4.3 billion [$4.989 billion] Boehringer Ingelheim + $1.704 billion Lilly); $13.037 billion in 2024 (€8.357 billion [$9.696 billion] Boehringer Ingelheim + $3.341 billion Lilly)[10]

> Darzalex® (daratumumab) and Darzalex® Faspro (daratumumab and hyaluronidase-fihj)
Johnson & Johnson
INITIAL U.S. APPROVAL: 2015 / 2020
REVENUE: $6.776 billion in Q1-Q2 2025; $11.670 billion in 2024[11]

> Cosentyx® (secukinumab)
Novartis
INITIAL U.S. APPROVAL: 2015
REVENUE: $3.163 billion in Q1-Q2 2025; $6.141 billion in 2024

> Shingrix (Zoster Vaccine Recombinant, Adjuvanted)
GlaxoSmithKline
INITIAL U.S. APPROVAL: 2017
REVENUE: £1.720 billion ($2.299 billion) in Q1-Q2 2025; £3.364 billion ($4.497 billion) in 2024

References available online.

See all the recent A-Lists
GENengnews.com/A-lists

Bring on the BioIndustrial Bucks: Growing America's Bioeconomy

By Henry Lee, PhD

Synthetic biology is ready for the next developmental milestone and America's leadership depends on getting the financing right

Henry Lee, PhD
CEO, Cultivarium

The future of American manufacturing isn't just digital—it's biological. As we stand at the precipice of the bioeconomy era, bridging the gap between laboratory innovation and industrial-scale production has never been more critical. Over the past two decades, synthetic biology has matured from an academic curiosity into a credible platform for manufacturing materials, foods, therapeutics, and fuels. Yet despite technical advances in DNA synthesis, strain engineering, and fermentation control, the financing structures and how we reward progress still lag behind.

Venture capital (VC) dollars are harder to raise for capital-intensive projects. Corporate partners want de-risked access to innovation, and startups need intermediate liquidity to avoid selling out too early. The current model forces brilliant academics with breakthrough technologies to become experts in industrial manufacturing overnight or watch their innovations die in the lab.

Borrowing a familiar framework

The Biobucks model that transformed pharmaceutical partnerships offers a powerful framework for accelerating bio-industrial manufacturing, creating a new paradigm where large corporations and nimble startups combine forces to compete globally and help secure America's technological leadership.

Biobucks are a familiar concept in the pharmaceutical industry, but mostly unfamiliar territory in industrial biotech. Biobucks refer to a large sum of potential money in a licensing or collaboration agreement between big pharma companies and smaller biotech startups, tied to defined R&D and commercial milestones. In traditional Biobucks deals, only six percent of the total partnership value is paid upfront, with the remaining contingent on achieving specific milestones. In Q1 of 2024, pharmaceutical companies provided $2.28 billion of upfront cash to smaller startups, which is 35% of the $6.5 billion that venture capitalists invested in startups.

A typical pharma deal might include:

- $5M upfront for early-stage IP
- $10M upon starting a Phase I clinical trial
- $50M for completing a successful Phase III clinical trial
- Royalties on future drug sales

This approach has generated remarkable market-driven progress, such as Pfizer's $700 million Biobucks deal across 10 programs with Flagship Pioneering. These partnerships work because they solve fundamental misalignments while managing the high failure rates inherent in biotechnology development.

Yet biomanufacturing has no equivalent. Most deals fall into one of three buckets: fee-for-service R&D, equity-based partnerships, or long-term supply agreements. These are simple to execute but aren't built for staged innovation and tangible outcomes along the way. For a startup engineering a novel microbe to produce a commodity chemical or climate-smart polymer, there's no standard framework to capture intermediate value creation. As a result, too many promising strain engineering programs stall after lab-scale proof-of-concept.

Why adopt BioIndustrial Bucks now?

It's time we introduce BioIndustrial Bucks (BIBs), milestone-based deal structures tailored to the realities of industrial

biotech and scaled to meet the moment. The window for American leadership in bio-industrial manufacturing is narrowing. China's substantial government investments in biotechnology and the EU's comprehensive biotech strategy announced in March of 2024 demonstrate that international competitors recognize the strategic importance of this sector. The United States must leverage its unique advantages—world-class research institutions, an innovative startup ecosystem, and scalable industrial manufacturing capabilities—through systematic BIB partnership approaches.

BIBs offer a compelling path forward for the symbiotic relationship between biotech startups and their corporate counterparts to flourish. These milestone-based partnerships empower academics and entrepreneurs to focus on breakthrough biology with the support of non-dilutive funding and corporate partners' decades of manufacturing expertise and market understanding. For corporate partners, this structure limits upfront risk while gaining access to cutting-edge innovation.

Secrets of a successful BIB model

While the milestone Biobucks model is an established structure, it needs adaptation for bio-industrial manufacturing. Introducing BioIndustrial Bucks as a standardized approach creates alignment, scalability, transparency, and risk distribution. The successful BIB model has three essential components:

1. Adapted financial structuring

Unlike pharmaceutical development with its well-established deal structures and clinical trial phases, bio-industrial partnerships must navigate different risk profiles, timelines, and milestones that warrant payout. For example, payment milestones shift from clinical endpoints to manufacturing metrics: pilot plant demonstration at 500-2,000 L scale, cost-reduction targets achieving competitive production economics, and regulatory approvals for new bio-based chemicals or materials.

Imagine a fermentation startup partnering with a global corporation like Cargill to make a drop-in bio-based ingredient. Instead of a one-time service fee or vague revenue share, the deal could be structured like this:

- $250K for 10 g/L titer in shake flask
- $1.5M upon a successful tech transfer to 300 L pilot plant
- $3M for achieving <$3/kg cost projection at 10,000L scale
- $5M + 2% royalty for delivery of the first 10-ton shipment
- Environmental, Social, and Governance (ESG) bonus of $1M as a result of avoidance of 1,000 metric tons CO_2

2. Corporate technical expertise and resources

The technical knowledge sharing and scalable resources that large corporations bring to a BIB collaboration are an essential part of the mix. Large industrial companies possess irreplaceable assets for biotech scale-up, including decades of expertise and process optimization, access to waste feedstocks, expansive testing facilities, and supply chain integration. Cargill's partnership with ENOUGH and BASF's acquisition of Verenium weren't just financial transactions—they exemplify how specialized knowledge and infrastructure can be leveraged to achieve cost targets and accelerate progress in bringing cutting-edge bio-industrial applications to market.

3. Government involvement

The federal government already provides powerful institutional frameworks for sophisticated risk management, tax-incentivized funding programs that are designed to complement private sector initiatives, and policies to catalyze bio-industrial partnerships.

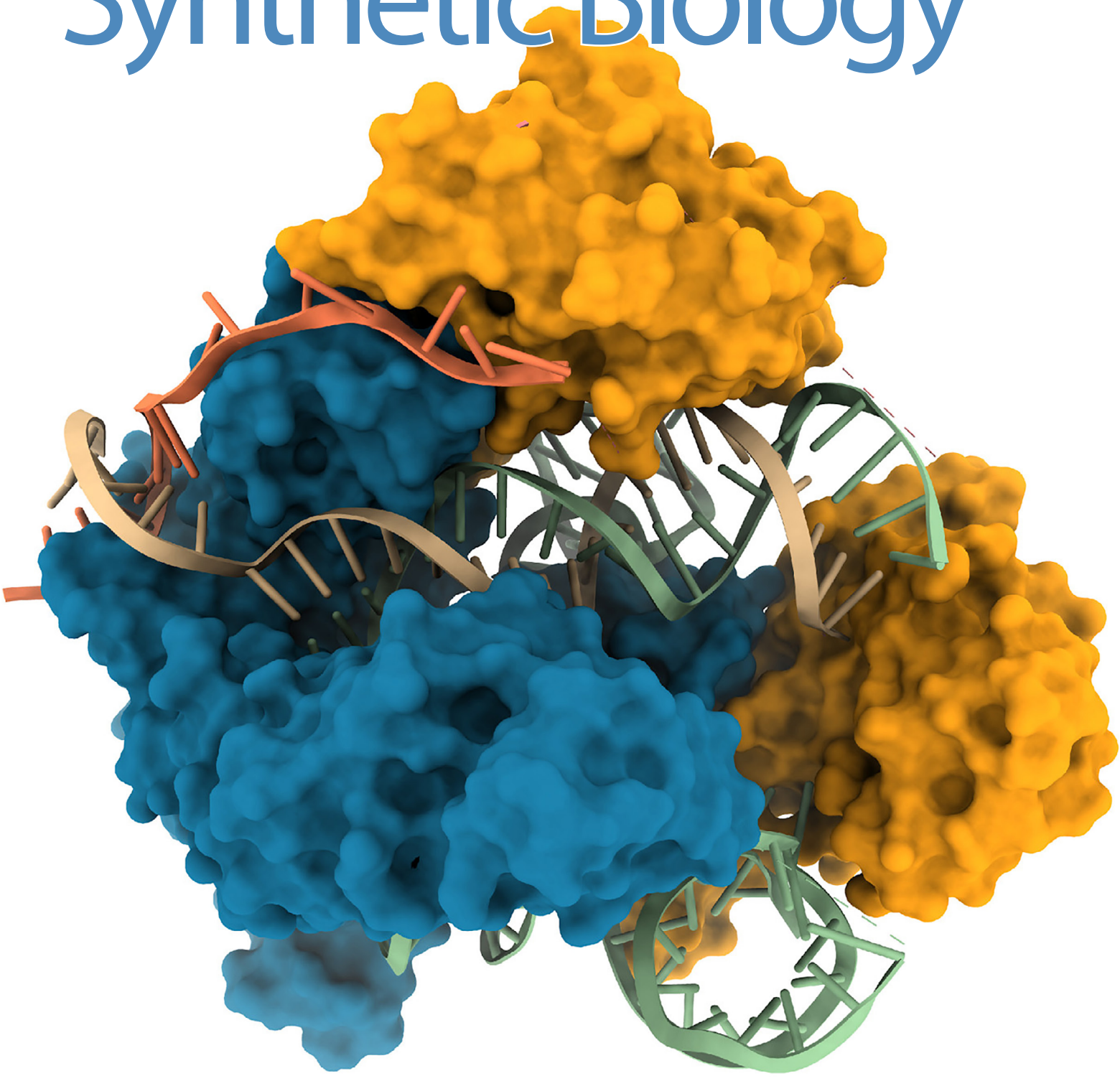
On the risk-management front, the Department of Energy's TRL framework, combined with NIIMBL's Biomanufacturing Readiness Levels (BRLs), provides systematic approaches to evaluating technical progress. Additionally, the DOD's Manufacturing Readiness Levels (MRLs) address scale-up challenges specific to

See Point of View on page 47

DrAfter123 / Getty Images

Drug Discovery

Biopharma Embraces Synthetic Biology



Applying new tools from cell engineering to compact CRISPR and drug design

By Tiffany Yesavage, PhD

Synthetic biology—an emerging and often debated field—involves the application of engineering principles to biological systems. While its definition has evolved over time, the European Commission today defines synthetic biology as the use of science, technology, and engineering to facilitate "the design, manufacture, and/or modification of genetic materials in living organisms."[1]

Over the past two decades, synthetic biology has fueled advancements across a broad range of disciplines, including agriculture, bioremediation, biofuel production, and chemical manufacturing. Today, it has begun to drive innovation in biopharmaceuticals. *GEN* spoke with four companies to explore how they are leveraging synthetic biology in their work.

CRISPR for hard-to-reach tissues

Trevor Martin, PhD, cofounder and CEO of **Mammoth Biosciences**, explains that CRISPR originates from the immune system of microorganisms. And while a wide variety of CRISPR systems exist in nature, the first one discovered involved a protein called Cas9. "Fortunately, CRISPR-Cas9 happens to be a great system," he notes. "But it has a lot of real limitations."

Martin emphasizes how Mammoth—spun out of the Doudna lab at the University of California, Berkeley—invested in novel CRISPR systems early on. "The real magic happened when we decided to go to nature to find all of these wacky CRISPR starting points in microbes," he says. From there, the company employed engineering techniques to enhance these proteins, utilizing machine learning and high-throughput liquid-handling robots to achieve this goal.

What are the advantages of having so many CRISPR systems? According to Martin, Mammoth has developed versions that use proteins a third the size of Cas9 or smaller. These ultra-compact systems are particularly well-suited for delivering gene therapies to hard-to-reach tissues, such as the brain and muscles.

A second advantage of ultra-compact CRISPR systems is that they enable many types of edits. While classic CRISPR editing introduces a double-stranded break, Martin stresses that ultra-compact CRISPR systems allow for the delivery of more complex machinery for more subtle edits—such as the addition or deletion of base pairs.

Martin highlights a Mammoth program called MB-111, which knocks out a gene called APOC3 in the liver that is associated with triglyceride disease. He notes that the program is on track for clinical trials.

Ultimately, Martin sees a rare opportunity to grow Mammoth into a $100 billion company. He explains that once a given CRISPR system proves effective for a specific disease in a particular tissue, only the guide RNA needs to be changed for the next indication. "This is a platform where, once you build one therapy, the second therapy gets easier—which is very different from traditional small-molecule drug discovery," he says.

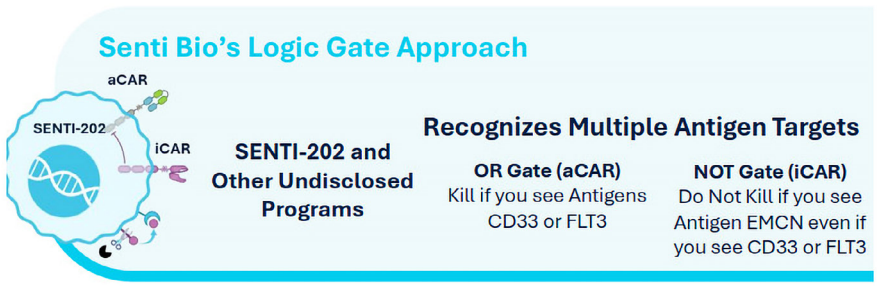
"When you think of genetic diseases, you think of dystrophies, Alzheimer's, and Parkinson's. These diseases are all muscle and CNS-related," he notes. "And Cas9 isn't really effective because it is too big to be delivered there." In contrast, the company has recently demonstrated very effective muscle editing with an ultra-compact CRISPR system called NanoCas.

Martin is optimistic about the possibility of finally tackling rare diseases of the brain and muscles over the next 10 years with Mammoth's technology. "We have a shot, which is crazy. I think there is a real shot at treating all diseases where we know exactly which genes to change."

Programmable medicines

Timothy Lu, MD, PhD, co-founder and CEO of **Senti Bio**, highlights the challenges associated with most existing cancer treatment modalities—such as T-cell

Left. The ultra-compact NanoCas from Mammoth Biosciences is an asymmetrical homodimer. [Mammoth Biosciences]



SENTI-202 from Senti Bio utilizes both an OR gate and a NOT gate to selectively target cancer cells while sparing healthy cells. [Senti Bio]

engagers, antibody-drug conjugates, and traditional CAR T-cell therapies.

"These treatments rely on recognizing a single cancer target that needs to be expressed on cancer cells but not healthy cells," he notes. "However, if these targets are not clean enough—as is often the case in blood cancers and solid tumors—there will be off-tumor killing, leading to side effects and preventing good cancer efficacy."

This is where gene circuit technology comes into play. Lu explains that gene circuits are another way of applying engineering principles to biology. "They are like computer programs written in DNA that enable cells to make decisions in the body to treat disease more precisely."

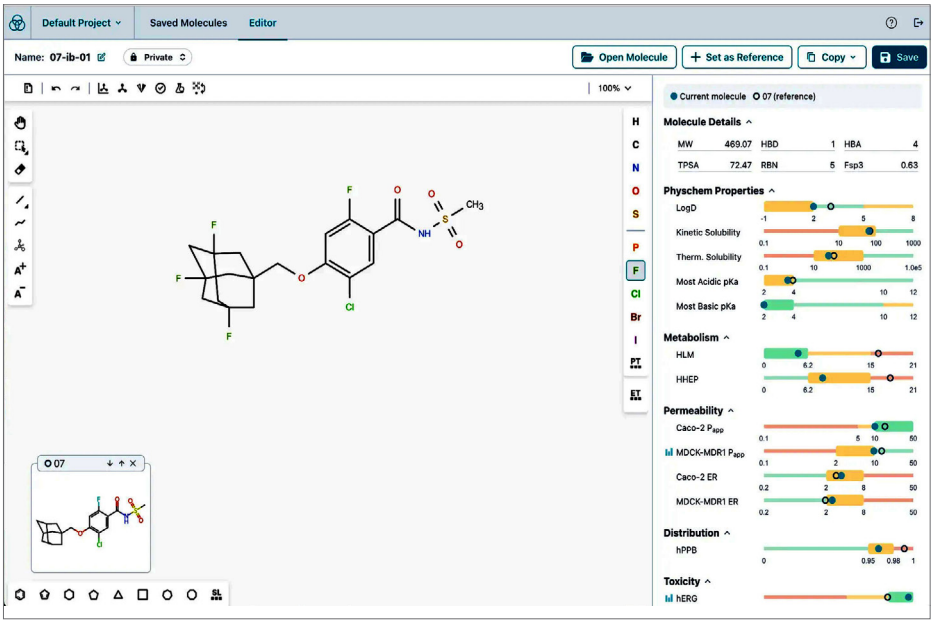
He highlights a specific type of gene circuit, called the "logic gate," which enables selective killing of cancer cells while sparing healthy ones. "Imagine this as a precise and smart missile that only hits military vehicles while avoiding civilian ones," he explains.

Senti Bio's lead program, SENTI-202, is a logic-gated cell therapy that programs natural killer cells to target heterogeneous cancer cells associated with acute myeloid leukemia (AML).

Lu explains that one of SENTI-202's chimeric antigen receptors is designed to recognize CD33, while the other recognizes FLT3—two markers commonly found on AML cancer cells. In this system, an "OR gate" instructs SENTI-202, "Kill if either CD33 or FLT3 or both are detected." This logic-based approach enhances the ability to recognize and eliminate malignant cells that express one or both markers, enhancing overall cancer killing.

However, both CD33 and FLT3 can also be found on healthy cells. To avoid toxicity against them, SENTI-202 recognizes EMCN, a marker found on healthy bone marrow stem cells. In this case, a "NOT gate" tells SENTI-202, "Do not kill if you see the EMCN antigen, even when CD33 and FLT3 are present."

SENTI-202 is currently in a Phase I clinical trial for relapsed/refractory AML and other related indications. As summarized in a recent conference, SENTI-202 is well-tolerated, and multiple patients have experienced complete remissions, with maximum durability reported beyond eight months.



Inductive's AI models simulate wet lab experiments in real-time, allowing scientists to optimize molecular designs virtually. AI models explore millions of designs to prioritize the best ones for experimentation. [Inductive Bio]

"Correlative data from patients showed targeted killing of AML blasts and AML leukemia stem cells and protection of healthy bone marrow stem cells, consistent with our logic gate mechanism of action," he notes.

Lu foresees additional applications for Senti Bio's programmable gene circuits, including solid tumors, autoimmune diseases, and gene therapy.

Drug discovery, engineered

The future of drug discovery will feature less trial-and-error work and more engineering approaches, predict Josh Haimson, co-founder and CEO of **Inductive Bio**, and John Androsavich, PhD, general manager at **Ginkgo Datapoints**.

"Synthetic biology is best known for enabling rapid design cycles in engineered organisms," notes Androsavich. "However, we're extending that philosophy to small-molecule drug discovery, which is still deeply rooted in biology." More specifically, this means programming biology with software principles—including designing, testing, learning, and iterating.

In traditional drug discovery, scientists typically begin by formulating a hypothesis about how a molecule might interact with a specific biological target. They then spend weeks or even months synthesizing the molecule and conducting experiments to assess its effects. The results of these experiments inform future hypotheses.

Haimson and Androsavich note that lab-in-the-loop workflows follow the same principles as traditional drug discovery. However, they use AI and automation to significantly expand the number of hypotheses that can be explored and the speed at which they can be tested.

With a lab-in-the-loop approach, AI models explore millions of ideas virtually and prioritize the most informative molecules to test in the lab. Those molecules are then rapidly synthesized and tested using lab automation, and the results

from those experiments are fed back into the AI models for learning. This loop runs continuously, making each round of design smarter.

Haimson and Androsavich highlight a three-way partnership that is underway between Inductive Bio, Ginkgo Datapoints, and **Tangible Scientific**. The goal is to provide a lab-in-the-loop infrastructure that will be available to the entire biopharma industry. As part of this partnership, Inductive will provide AI models for small molecule drug discovery, Ginkgo will bring high-throughput, automated lab assays to test those molecules, and Tangible will orchestrate the secure storage and handling of samples.

"Lab-in-the-loop research is not just about making old processes faster," emphasizes Haimson. "Instead, the goal is also to enable the discovery of better, safer, and more innovative drugs. By exploring massive amounts of ideas and learning directly from experimental feedback, our platform can suggest directions that teams wouldn't have thought of."

Finally, Haimson notes that nearly 40% of biotech companies will be facing cash flow shortages by the end of 2025.[2] "Our platform helps them maintain competitive drug discovery capabilities without the massive platform investments that were once required."

Engineering microbes

Andy Budde, business development associate for **Isomerase**, stresses the growing importance of engineered microbial biology. "The goal is to treat living cells as programmable platforms by combining biology with the tools of chemistry, engineering, and computer science," he says.

He explains that Isomerase's clients typically approach the company with the intention of modifying and scaling enzymes, proteins, peptides, small molecules, and natural products. The company supports the development of each client's ideas into real-world products for clinical and commercial use.

> "I think there is a real shot at treating all diseases **where we know exactly which genes to change.**"
>
> —Trevor Martin, PhD
> Co-founder and CEO
> Mammoth Biosciences

"At Isomerase, we have worked extensively with natural products, which remain a rich and underexplored source of active pharmaceutical ingredients," notes Budde. However, the company also employs engineering principles to design new possibilities—ranging from breakthrough medicines to more sustainable production methods, such as biocatalysis.

Isomerase employs a range of tools to modify microorganisms and molecules, including machine learning and strain engineering, in which microbial hosts are reprogrammed at the genetic level to improve yields, robustness, and scalability. The company's machine learning-driven EvoSelect® platform enables the directed evolution of enzymes into more efficient and scalable biocatalysts.

Isomerase also employs fermentation to improve the commercial viability of biopharmaceutical products. "The use of microbes offers several advantages over traditional chemical reactions," Budde says. "Namely, it doesn't require harsh solvents or surfactants, making it more cost-effective and environmentally friendly."

Does Isomerase prioritize sustainability, innovation, or efficiency? "In practice, these goals are interconnected," says Budde. "A sustainable process is most often more efficient, and new biological routes can unlock compounds that were previously inaccessible." GEN

References

1. Heidari R, Shaw DM, Elger BS. CRISPR and the rebirth of synthetic biology. *Sci Eng Ethics*. 2017;23(2):351-363. doi: 10.1007/s11948-016-9768-z.

2. Focus on fundamentals to bounce back. EY Biotech Beyond Borders Report 2025. EY Insights. Page 7. ey-beyond-borders-2025-report-final.pdf.

Automated lab foundry at Ginkgo Bioworks' Boston headquarters. Proprietary reconfigurable automation carts with a modular configuration are used to run diverse lab data generation workflows for different clients. [Ginkgo Bioworks]

Turbocharging Cas9's Nuclear Entry

By Christopher Doyle, PhD

Gene editing efficiency boosted by new nuclear localization signal strategy

Christopher Doyle, PhD
Senior Director, IBC Services
WCG Clinical

Advanced engineered cell therapies require gene editing tools that are both precise and efficient. In recent years, CRISPR-Cas9 has emerged as the gold standard for editing genes with greater precision than older techniques. Unlike viral vectors that randomly integrate DNA into the genome, Cas9 and similar endonucleases cut DNA at specific sites, allowing for controlled modifications. However, CRISPR-Cas9's full potential in clinical applications remains limited by a fundamental challenge: getting enough Cas9 protein into the cell nucleus, where it can reliably modify cellular DNA.

Most current approaches rely on adding nuclear localization signal (NLS) motifs to the ends of Cas9 to facilitate nuclear entry. However, this method is inefficient, and much of the Cas9 that is provided to cells never reaches the nucleus. Addressing this inefficiency is critical for successful therapeutic applications, where any enhancement could mean more effective treatments.

A recent publication by researchers at the University of California Berkeley's Innovative Genomics Institute unveils a clever solution to boost Cas9's nuclear entry—and thus its gene editing performance—by increasing the number of NLS motifs within the Cas9 protein.[1] Here, I highlight how this novel approach improves gene editing in human T cells and discuss its implications for the development of future cell therapies.

A new approach to nuclear delivery

Traditional Cas9 designs typically include one to three NLS motifs attached to the protein's C- and N-termini. The Berkeley team hypothesized that adding more NLS motifs to different areas of Cas9 could improve nuclear import, but simply extending the terminal tails with additional NLS motifs proved problematic. In line with prior experimental data, a Cas9 with six terminal NLS motifs showed poor expression yields, making it impractical for large-scale production.

Their innovative solution was to insert additional NLS motifs into internal loops of the Cas9 protein, where they would be more evenly distributed across the protein, rather than at C- or N-termini, which are located closely together in the protein's 3D structure.[2] By analyzing the protein's structure, they identified several surface-exposed loops where NLS insertions would be tolerated, allowing for the addition of NLS without compromising the protein's stability or activity.

Each hairpin internal NLS (hiNLS) module consists of two NLS motifs arranged in tandem, separated by flexible linkers. This tandem design ensures that if one motif temporarily detaches from the importin proteins that mediate nuclear entry, the other can still hold on, increasing the likelihood that Cas9 remains bound during transit into the nucleus. The team generated 15 different Cas9 variants with one to four hiNLS modules inserted, yielding variants with up to nine individual NLS motifs.

Testing in primary human T cells

To evaluate their hiNLS-Cas9 variants, the researchers tested their ability to edit primary human T cells, which are a cornerstone of many cell therapies, including chimeric antigen receptor (CAR) T cells. The team introduced gRNA-Cas9 ribonucleoprotein complexes (RNPs) targeting two clinically relevant genes: β2M (beta-2 microglobulin) and TRAC (T-cell receptor alpha chain). Disrupting β2M helps

create immune-evasive cell therapies by eliminating expression of major histocompatibility complex I (MHC-I) molecules on T cells, while loss of TRAC can prevent graft-versus-host reactions and make space for synthetic receptors in CAR T cells.[3]

The researchers delivered RNPs to cells using two methods: standard electroporation and a peptide-mediated delivery method (peptide-enabled ribonucleoprotein delivery for CRISPR engineering [PERC]), which relies on peptide-RNP complexes to facilitate cell entry.[4] Compared to electroporation, PERC is gentler and simpler, with less impact on cell viability and requiring no specialized equipment. The study's authors therefore used PERC as a surrogate for *in vivo* editing technologies—such as lipid nanoparticles or virus-like particles—where preserving cell viability is critical and the editing window is limited due to transient RNP availability.

When multiple hiNLS modules were combined in one Cas9, editing rates improved significantly. For example, a Cas9 with two NLS module inserts (s-M1M4) delivered via electroporation knocked out the *β2M* gene in over 80% of T cells, compared to about 66% with traditional Cas9. Using the PERC method, several multi-hiNLS constructs achieved 40–50% knockout efficiency, whereas the control managed around 38%. Throughout testing, T-cell viability after editing remained unaffected by the extra NLS, which is reassuring for therapeutic applications. Interestingly, a direct association between the number of NLS inserts and editing efficiency was not observed. However, variants rich in c-Myc-derived NLS outperformed those using SV40 NLS signals, suggesting that NLS sequence quality matters at least as much as quantity.

Key advantages for the clinic

This study demonstrates several practical advantages of hiNLS-Cas9 for therapeutic development:

- ***Higher Editing Efficiency:*** By addressing the nuclear entry bottleneck, hiNLS-Cas9 can achieve higher editing percentages in T cells than conventional Cas9. This suggests other difficult-to-edit cell types could also benefit from an hiNLS boost, making both experiments and therapies more effective. PERC-based delivery of hiNLS-Cas9 variants resulted in editing efficiencies similar to those seen with electroporation. Since PERC is less cytotoxic than electroporation, this could mean even greater percentages of edited cells from the same amount of Cas9, also critical for scalability.

- ***Maintained Protein Yield:*** Unlike Cas9 with multiple terminal NLS motifs, the hiNLS variants remained easy to produce, with recombinant yields of 4-9 mg per liter, comparable to unmodified Cas9. This means labs and companies can manufacture hiNLS-Cas9 at scale without special techniques, which will be crucial for clinical translation.

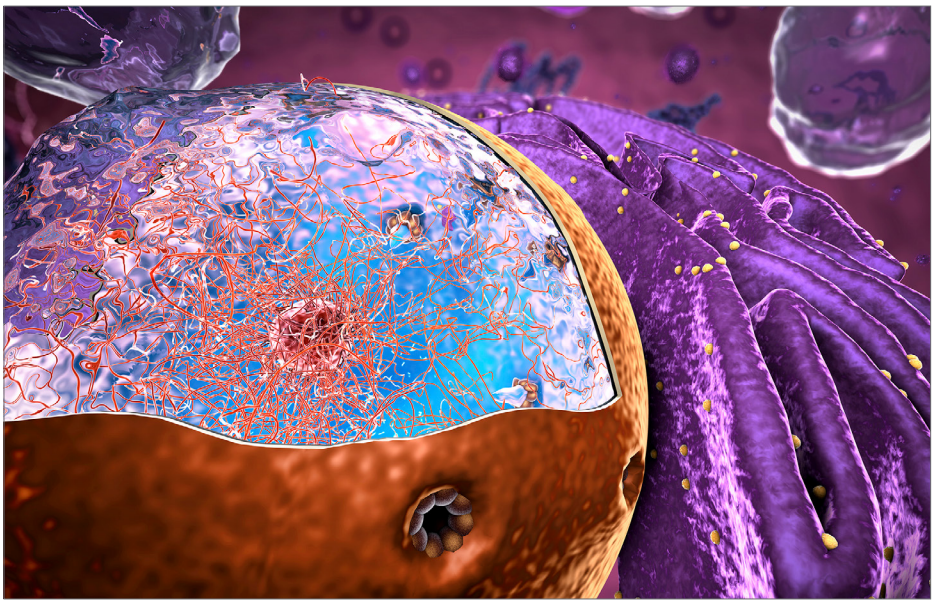
- ***Rapid Action for Transient Delivery:*** The improved nuclear localization is especially valuable for transient delivery formats like RNPs or mRNA, where the editing window is brief. The results showed hiNLS-Cas9 can capitalize on that short window, potentially reducing the required dose or increasing editing achieved per dose.

For cell therapy manufacturing, where editing efficiency directly impacts production costs and timelines, these improvements could be transformative. More specifically, current CAR T manufacturing processes face challenges with consistency and yield, so higher editing rates could help address these issues.

Future directions and combinations

Combining the hiNLS-Cas9 method with parallel advances multiplies the possibilities. Scientists are exploring virus-like particles and lipid nanoparticles to deliver Cas9 RNPs directly into patients for *in vivo* editing.[5] Such *in vivo* approaches often suffer from low delivery rates to the nucleus, but an NLS-boosted Cas9 might increase editing in the few that do arrive. Another complementary avenue is

See Thought Leader on page 32



3D illustration of the nucleus inside a eukaryotic cell. The nucleus contains the cell's genetic information in the form of DNA which is complexed with proteins and stored as chromatin. Successfully targeting and gaining entrance to the nucleus is an ongoing challenge of CRISPR-based therapies. [Christoph Burgstedt / Science Photo Library / Getty Images]

OMICS

Mass Spec Brings Multiomics Into Sharper Focus

Christoph Burgsted/Science Photo Library/ Getty Images

By Caroline Seydel

Improvements in sensitivity, specificity, and accurate quantitation allow researchers to glean valuable information from hundreds of samples in record time

Clinical and translational research is increasingly turning to molecular studies, such as proteomics and metabolomics, but research is limited by the availability of tools to catalog the many thousands of molecules in a single blood sample with high accuracy, sensitivity, and speed. Mass spectrometry can provide quantitative peptide-level information, but until recently has lacked the throughput to accommodate large-scale studies. Now, new instruments, sample preparation technologies, and data processing platforms are enabling researchers to collect proteomic and metabolomic data from patient populations on a scale previously unheard of.

"If you look at the history of mass spectrometry-based proteomics, the rate-limiting step has almost always been the mass spectrometer," says Daniel Hermanson, PhD, director of product management at **Thermo Fisher Scientific**. Two years ago, Thermo introduced the Orbitrap Astral MS, which boosted throughput by about a factor of four, Hermanson says, enabling researchers to scan 180 samples per day. Now, the company has unveiled a new instrument, the Orbitrap Astral Zoom MS, which is not only faster but also more sensitive.

"It not only allows you to do these very high-throughput studies, but it brings additional depth and accurate and precise quantitation into play, which allows us to go much deeper, faster," Hermanson says. The previous Orbitrap Astral MS can measure 180 proteomics samples per day and return results on around 8,000 different proteins. Using the same protocol, Hermanson says, the Orbitrap Astral Zoom MS can measure 8,600 proteins. "Alternatively, you could go to about 300 samples per day on Orbitrap Astral Zoom and get that 8000 protein number."

The Orbitrap Astral Zoom MS achieves this improvement thanks to two big changes: an increased scan rate (from 200 Hz to 270 Hz) and pre-accumulation of ions. With pre-accumulation, the instrument adds an extra ion-capturing step in parallel. This provides more ions at the 200 Hz scan rate or a similar number of ions at the faster scan rate.

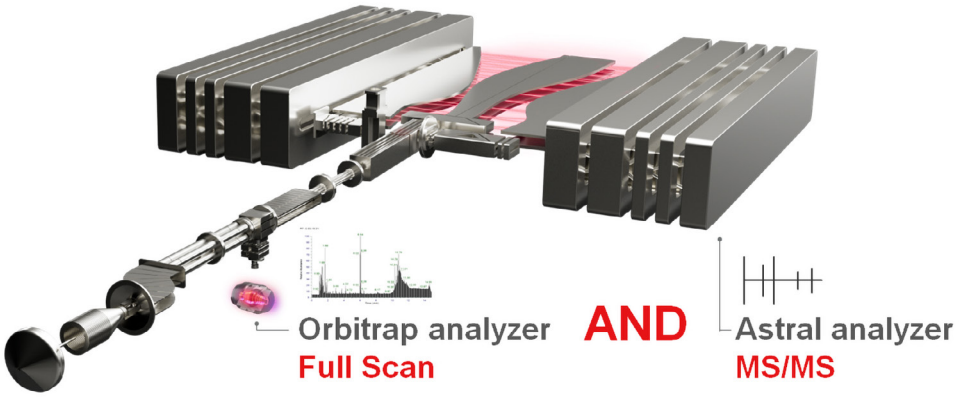
Having an instrument capable of running hundreds of samples per day won't increase throughput if it simply shifts the bottleneck to the data processing step. On the software side, Thermo Fisher is increasing the capabilities of its Ardia Platform to efficiently manage and process data as it's collected. "As soon as that raw data file is acquired, it starts processing in the data processing software," Hermanson explains. "Now you're not waiting for every sample to acquire before starting the processing." The Ardia platform also aims to streamline collaboration by enabling the data to be read by third-party software, directly shared via a web browser interface, or deposited into public databases.

"It's really an exciting time to be in proteomics," Hermanson says. "It's inspiring to see what people are able to do with this technology." For example, he says, Yu-Ju Chen, PhD, distinguished research fellow at Academia Sinica in Taiwan, used the Orbitrap Astral Zoom mass spectrometer in her translational research focused on lung cancer screening. To screen 6,000 patients for protein biomarkers would have taken 1,000 days using existing mass spec instruments, but with the Orbitrap Astral Zoom, it would take 100 days. "That is so exciting that we can take proteomics into the scale that's required to make a true impact in the real world," Hermanson says.

Nanoparticles and the proteome

Once the scanning and data processing steps are sped up, the other potential bottleneck is sample preparation. While mass spectrometry proteomics can be applied to neat plasma, the tremendous dynamic range of proteins means that highly abundant proteins can mask the detection of rarer, but more biologically interesting, proteins. Immunodepletion methods are often used to enrich for low-abundance proteins, but these are too labor-intensive to scale and do not always produce reproducible results.

The Proteograph™ product suite from **Seer** leverages unique properties of nanoparticles to rapidly and reproducibly extract peptides from a sample



The Thermo Scientific Orbitrap Astral Zoom Mass Spectrometer is designed to achieve the next generation of breakthroughs with upgraded hardware and software capabilities to deliver increased flexibility, faster throughput, deeper coverage, higher sensitivity, and accurate and precise quantitation.

Having a fully automated instrument to extract proteins from liquid samples means the results are highly reproducible compared to a manual protocol. The Proteograph system from Seer can prepare 80 samples for mass spectrometry analysis in one hour. [Seer]

via a completely automated workflow. "The robustness and the reproducibility of these are incredible and suitable for doing large-scale studies," says Omid Farokhzad, MD, CEO of Seer.

Proteograph begins with multiplexed, engineered nanoparticles designed to collect a broad range of proteins from a liquid sample, including plasma, urine, or cell lysate. Proteins in the sample accumulate around the nanoparticle, creating a shell called a protein corona, and this corona forms in a specific, predictable way. "These nanoparticles are designed specifically for maximum capture across the entire dynamic range," Farokhzad says. "They capture the abundant proteins, but they also capture the least abundant proteins. Essentially, it compresses the dynamic range, but it does it quantitatively, and it does it reproducibly." The entire process is automated, meaning that the user can put a biological sample directly into the instrument without any depletion or fractionation, and in about five hours, the peptides are ready to be analyzed in the mass spectrometer.

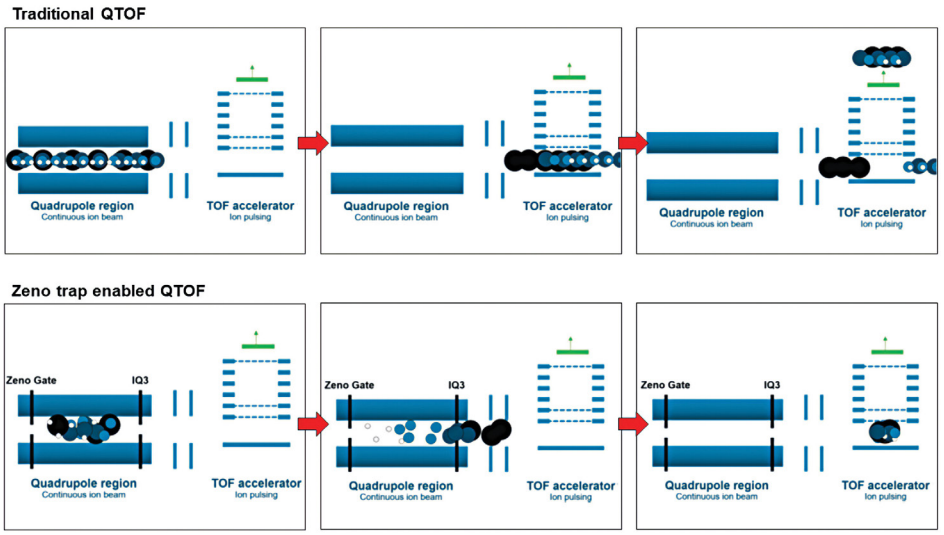
The instrument can process 80 samples at a time. When Seer launched in 2017, Farokhzad says, the largest deep-plasma proteomic work ever published analyzed just 48 samples with coverage of 1850 proteins. Today, Seer has multiple customers using Proteograph to process thousands of samples with coverage of more than 8000 proteins.

For example, in 2020, Seer spun out **PrognomiQ**, a multiomics company pursuing early cancer detection, using data generated by Proteograph to identify biomarkers. In a paper in *medRxiv*, PrognomiQ reported that their lung cancer early detection blood test achieved 89% sensitivity and 89% specificity, using biomarkers derived from DNA, RNA, proteins, and metabolites.

"They did unbiased proteomics to a depth of about 13,000 proteins in their study looking at 2500 individuals to identify biomarkers of cancer," Farokhzad says, adding that the test is expected to launch in late 2025. "That test is the first clinical application of our platform as a commercially available product."

More than proteins

Increasingly, scientists are turning to small molecule analysis for biomedical insights, increasing demand for instruments that can catalogue metabolites accurately and at scale. Earlier this year, **SCIEX**, an operating company of **Danaher Corporation**, launched its ZenoTOF 8600 system, which improves sensitivity by up to a factor of ten over the previous model. Additionally, "it offers a unique combination of state-of-the-art technologies that expand its application to all the different omics workflows," says Katherine Tran, senior manager of global market development for proteomics at SCIEX. "The thing with the ZenoTOF is it's so versatile."



In a traditional quadrupole TOF instrument, loss of ions reduces sensitivity. The Zeno trap design allows the ions to accumulate, then releases them in roughly reverse mass order, improving sensitivity up to 10x over previous TOF mass spectrometers. [SCIEX]

How Proteintech's New AI is Transforming Reagent Selection

In an industry first, Proteintech has unveiled Able AI, an artificial intelligence (AI) platform designed specifically to assist scientists in selecting research reagents and optimizing experimental design. By combining deep antibody validation data with an intuitive AI interface, Proteintech's new tool aims to transform how researchers plan experiments, helping them move from target identification to data generation faster than ever before.

From complexity to clarity: Solving the reagent selection problem

Selecting the right antibody or reagent is one of the least automated steps in biological research. With millions of reagents to choose from, each with nuanced characteristics, researchers often face an overwhelming number of options and are left unsure about which product suits their needs best.

Proteintech, a manufacturer of rigorously validated antibodies and recombinant proteins, recognized this pain point. The company's extensive product metadata and validation archives provided a natural foundation for AI-driven insights. Able AI represents the culmination of those efforts, leveraging the available datasets to create an online concierge service that guides scientists through reagent selection and experimental setup.

What Able AI delivers

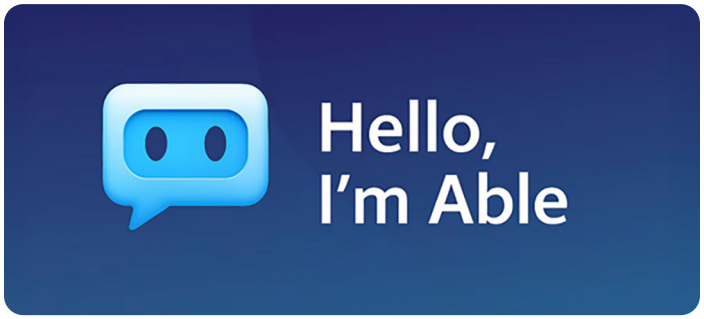
Able AI offers two key capabilities for life scientists:

1. Smart reagent recommendations

Using Proteintech's proprietary dataset, Able AI identifies which antibodies are most likely to perform well for a given target, species, or application. It can also provide recommendations for specific research areas, modifications, or pathways. To further support data transparency, Able AI can respond with product validation data, literature references, and links to supplementary resources on Proteintech's website.

2. Experimental support

Beyond product suggestions, the tool helps users design



Proteintech

experiments, recommending appropriate controls, sample types, and validation strategies.

"Able AI delivers tailored product recommendations and experimental design support, reducing the barriers between product data and discovery. Researchers can now spend less time searching for the right product and more time at the bench," said Jason Li, PhD, CEO of Proteintech.

Empowering scientists through AI

Proteintech's launch of Able AI marks the first time a reagent manufacturer has deployed an AI assistant that directly integrates with its product catalog and validation data.

For many labs, Able AI can serve as a "digital lab partner," turning complex reagent databases into actionable insights. The system will evolve into a community-driven model, learning from publication data and experimental outcomes. Scientists can also receive responses in their local language, as Able AI is multilingual.

The introduction of Able AI also highlights a broader trend in life sciences—growing interest in applications of automation and AI to research workflows. As more companies explore these technologies for product discovery and protocol design, Proteintech's early leadership offers a blueprint for innovation and customer empowerment.

In the words of Li, "The 3D epitope mapping initiative was the first AI-driven project we completed to provide scientists with deeper insight on their antibody. Able AI builds on that foundation, giving the customer practical, real-time guidance on how to design their experiment." ■

The platform is now live and freely accessible via

ptglab.com/Able

proteintech®

The ZenoTOF 8600 system starts with the triple quadrupole front-end ion source and ion guide that SCIEX is known for and combines it with a Zeno trap-enabled QTOF and a new optical detector. It also includes Mass Guard, a feature that uses T-bar electrodes to filter out contaminating ions and create a cleaner ion beam, and tunable electron activated dissociation (EAD), which provides a range of different free electron-based fragmentation mechanisms within one device. Finally, the ZenoTOF 8600 system includes ZT Scan DIA 2.0, which covers a larger mass range than the previous version. "Together, the extended mass range provided by ZT Scan DIA 2.0 and tunable, higher-energy EAD cell enable comprehensive analysis of both small and large molecules, such as immunopeptides and glycopeptides," Tran says. It's also fast: with ZT scan DIA 2.0, the instrument can achieve a scan rate of 858 Hz, "making it the fastest QTOF system for high resolution accurate mass," Tran says.

Tran adds that the company has not neglected the user experience. "At the end of the day, it's not just the improvements in the instrument that will benefit a user, it's the usability of it as well," she says. "Enhanced functionality in SCIEX OS acquisition software improves the user experience by providing real-time data quality metrics, method optimization, and system performance monitoring."

Small molecules, big impact

Bruker Corporation is also moving into the metabolomics space, expanding on its trapped ion mobility spectrometry (TIMS) technology to create the timsMetaboTM platform, specifically designed to tackle small molecule identification and quantification.

"TIMS technology has done very well in proteomics, and the company wants to extend that proficiency across the omics space," says Matthew Lewis, PhD, vice president of metabolomics and lipidomics at Bruker. "Through changes to the hardware combined with new acquisition modes, we've been able to extend the mobility range that we can transmit, and that enhances greatly the sensitivity of the system for small molecule applications."

Lewis says that TIMS technology has key benefits that make it well-suited to small molecule analysis. Metabolites, as a group, are much more chemically diverse than proteins. TIMS provides high resolution of molecules of similar or identical mass, allowing more selective measurement of quantities and cleaner MS/MS fingerprints. It also provides collisional cross section (CCS) measurements, an orthogonal measurement by which to validate an annotation. "CCS values are intrinsically, accurately predictable, unlike MS/MS fragmentation patterns, unlike LC retention times," Lewis says. "We can now say we think the annotation is correct based on mass, retention time, isotopic pattern, fidelity, all these things, and then we validate it by comparing the measured CCS to either a library or a predicted value."

Another unique feature of TIMS is that it orders the ions by CCS measurement and by mobility. "As a consequence of that, all the downstream components have some knowledge of what's coming and when," Lewis says. The timsMetabo includes the new Athena Ion Processor, which can use this knowledge of the incoming ions to optimize their transmission to the TOF, boosting sensitivity.

"The timsMetabo comes from a dedicated push to better serve the small molecule communities of metabolomics, untargeted screening, [and] bioanalysis," Lewis says. "My hope for this instrument is that people use it as a routine workhorse." GEN

Thought Leader Continued from page 27

engineering Cas9 for higher specificity. The authors noted a slight uptick in off-target activity at one known problematic site when using hiNLS-Cas9, likely because the extra NLS motifs help Cas9 remain bound to DNA longer. Merging high-fidelity Cas9 mutations with hiNLS could yield an enzyme that is both accurate and highly efficient.[6]

Looking ahead, the hiNLS-Cas9 strategy could be applied to other genome editors, such as Cas12a or base editors, which face similar delivery constraints. This work also underscores an important design concept: rather than oversimplifying an enzyme with just terminal tags, we can rationally modify it from within to balance performance and practicality. As gene editing moves toward multiplexed approaches where multiple genes are targeted simultaneously, the efficiency of each individual edit becomes increasingly important. Higher per-target efficiency with hiNLS-Cas9 could make complex multiplex editing more feasible, opening doors to next-generation cell therapies with sophisticated engineered functions.

By focusing on the often-overlooked aspect of nuclear localization, researchers have created a more efficient tool that could help accelerate the development of gene-edited cell therapies while potentially reducing manufacturing costs—a win for both developers and patients awaiting these innovative treatments. GEN

Christopher Doyle, PhD, is the senior director of IBC Services at WCG Clinical.

References available online.

ADVANCING THERAPEUTIC DISCOVERY

Through hiPSC-Derived Systems

Human induced pluripotent stem cells (hiPSCs) have revolutionized biomedical research by offering a versatile, human-relevant platform for modeling biology and advancing therapeutic development. Their ability to be generated from any somatic tissue, along with the potential for genome editing and differentiation into nearly any human cell type, makes them a powerful tool across multiple stages of the drug development process.

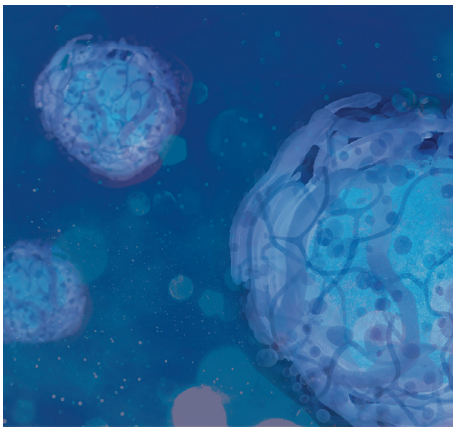
As the field evolves, the focus is shifting from initial adoption to the strategic integration of hiPSC-based models within existing drug development workflows—aiming to enhance decision-making throughout the pipeline.

Disease modeling & target identification

hiPSC disease models can be generated from individuals carrying disease-associated mutations or by introducing specific genetic variants into healthy reference lines. Importantly, these mutations can be corrected back to wild-type to create isogenic pairs, enabling precise and controlled comparisons. This genetic matching allows researchers to isolate and investigate the functional impact of genetic changes in a human cellular context, uncover dysregulated pathways, and identify molecular targets for therapeutic intervention.

Target validation

Once potential therapeutic targets are identified, hiPSC-derived models provide a robust *in vitro* platform for early-stage target validation. By manipulating gene expression or applying candidate compounds in disease-relevant, hiPSC-differentiated cell types, researchers can assess whether modulating a target produces meaningful changes in cellular phenotype or disease-associated markers. This step is essential for determining which targets are associated with disease and also actionable, enabling identification of priority targets for further preclinical drug development.



The Jackson Laboratory

Lead discovery

Once a target is identified, hiPSC-derived models can be used for compound screening and early-stage drug validation, offering a human-relevant platform for evaluating therapeutic candidates.

Leveraging genetically stable isogenic hiPSC panels—cells engineered to carry distinct mutations while sharing the same genetic background—enables direct comparison of drug effects across variants. This approach supports consistent application of growth and differentiation protocols, facilitates scalability, reduces variability, and enhances reproducibility, while allowing for precise interpretation of variant-specific responses.

Incorporating revertant controls, where engineered mutations are corrected back to wild-type, further strengthens target specificity by confirming that observed effects are mutation-driven and not due to off-target effects. Together, these strategies minimize confounding variables and support robust lead identification and prioritization.

Preclinical testing

In preclinical studies, hiPSCs complement traditional animal models by offering insights into human-specific biology. They are particularly valuable for modeling diseases that lack robust animal models, such as certain rare genetic disorders.

Using hiPSC lines to develop complex models—such as organ-on-chip systems—helps bridge the gap between simple *in vitro* assays and *in vivo* studies. These platforms provide more human-relevant assessments of drug efficacy, toxicity, and pharmacodynamics, ultimately reducing late-stage failures and increasing confidence in candidate selection.

Clinical translation

hiPSC models play a critical role in informing drug development by helping to identify predictive biomarkers, stratify patient populations, and anticipate variability in drug response. Lines derived from diverse genetic backgrounds can reveal population-specific effects that may not be captured otherwise, supporting the development of more inclusive and personalized therapies.

Looking ahead

As hiPSC technologies advance, their impact on drug development continues to grow. Innovations in differentiation, high-content phenotyping, and complex models are improving our ability to model patient-specific biology with greater precision and relevance—driving progress in discovery, validation, and translational research.

However, successful implementation hinges on the availability of high-quality hiPSC lines and standardized protocols to ensure data reliability and reproducibility. Resources like The Jackson Laboratory hiPSC catalog support this progress by offering well-characterized isogenic lines and validated protocols, helping researchers streamline workflows, improve reproducibility, and accelerate the integration of hiPSC-based systems into diverse therapeutic pipelines. ■

Artificial Intelligence

AI Models Enhance
the Drug Discovery Portfolio

Machine learning models driven by large-scale data continue to power diverse therapeutic modalities

By Fay Lin, PhD

Drug discovery has not yet had its "ChatGPT moment," according to Arman Zaribafiyan, PhD, head of product, AI simulation and platforms, at **SandboxAQ**, in an interview with *GEN*. "We can't rely only on machine learning models trained on text-based data to solve the world's most challenging problems. The cure for cancer is not written in Wikipedia," he said.

SandboxAQ is a spinout from the multinational technology conglomerate, Alphabet, seeking to advance large quantitative models (LQMs) for positive impact on society, including drug discovery applications. In contrast to large language models (LLMs), which train on text-based data, LQMs are grounded in physics to simulate real-world systems.

The 2024 publications of Google DeepMind's AlphaFold3[1] and RoseTTAFold All-Atom,[2] developed by the lab of Nobel Laureate David Baker, PhD, was a technological inflection point that expanded protein structure prediction capabilities from peptide chains to interactions with small molecules, nucleic acids, metal ions, and more.

These structural co-folding models predicted the "pose," or how ligands bind to their target protein, but had not yet made the advance of predicting binding affinity, or the strength of the interaction. Achieving accurate binding affinity predictions would provide a powerful alternative to resource-intensive experimental screens to cut discovery timelines and save costs.

Left. A Retro Biosciences scientist uses microfluidic technology to precisely study individual cells. The company is developing therapies for reversing age-related dysfunction.

Small molecules that bind

In June, researchers from the Massachusetts Institute of Technology (MIT), in collaboration with **Recursion**, the Salt Lake City-based AI drug discovery company that combined with Exscientia in 2024, announced the open-source release of Boltz-2. It demonstrated binding affinity predictions at newfound speed and accuracy to democratize AI-based small molecule drug discovery across the commercial landscape.

Boltz-2 was the top predictor of binding affinity at the December 2024 Critical Assessment of Protein Structure Prediction 16 (CASP16) competition for benchmarking state-of-the-art models in structural biology. In speed, Boltz-2 is reported to calculate binding-affinity values in just 20 seconds, a thousand times faster than free-energy perturbation (FEP) simulations, the current physics-based computational standard. The model is available under the highly permissive MIT license, which allows commercial drug developers to use the model internally and apply their own proprietary data.

Zaribafiyan emphasizes that the lack of data connecting protein-ligand structural complexes with pharmacokinetics (PK)—how the body affects a drug—and pharmacodynamics (PD)—how drugs impact the body—remains a main bottleneck in AI-based drug discovery. To address this gap, one solution is to generate synthetic training data using computationally predicted structures.

A few weeks after Boltz-2's release, SandboxAQ, in collaboration with Nvidia, announced the Structurally-Augmented IC50 Repository (SAIR), an open-access repository that leveraged the Boltz series of models to generate computationally folded protein–ligand structures linked to corresponding experimental drug affinity values.

SAIR contains over one million unique protein–ligand pairs and a total of 5.2 million 3D structures curated from experimental binding affinity databases ChEMBL and BindingDB, which were then computationally folded using Boltz-1x. (Boltz-1x is an augmented version of the biomolecular complex prediction model Boltz-1, which improves structures to respect physical laws and prevent distorted internal geometries). According to the SAIR technical report, 97% of the Boltz-1x folded structures passed the checks of PoseBusters, an established computational tool that evaluates biophysical plausibility.

While Boltz-2's training set includes data from ChEMBL and BindingDB, and by extension, all complexes contained in SAIR, other research groups have reported applying SAIR to their AI drug discovery efforts. According to Zaribafiyan, **Technetium Therapeutics** is using SAIR to build agentic AI models to identify drug candidates with a focus on oncological and immunological diseases, while researchers from Texas A&M University are generating foundation models that design novel ligands inside the pocket of a protein for therapeutic applications.

"You want to understand the pose if you're going to make additions or changes to the small molecule once you know that it's binding, but most of early drug discovery is 'does your molecule

bind or not?'," weighed in Ian Quigley, PhD, CEO of **Leash Bio**, in an interview with *GEN*. "The ability to predict [binding affinity] is important and we're grateful that the community is paying more attention."

Quality data, simple architecture

Leash is a Salt Lake City-based start-up with the mission of filling the small molecule drug discovery data gap. According to Quigley, life science datasets can be riddled with batch effects and technical noise, making it difficult for models to make accurate biological predictions.

"There's a famous data collection where they gathered horse photos from an equestrian commercial photographer. All the photos contained a watermark showing the name of the photography business in the corner," explained Quigley. "Turns out if you put the watermark on any photo, an AI model trained on that data will say it's a horse. Same goes for life sciences. There are many ways that watermarks can show up in your data."

Quigley argues that generating large, quality, datasets that screen millions of small molecules against hundreds of protein targets can enable strong predictive performance, even with modest model architectures.

In July, Leash announced Hermes, a small molecule–protein binding prediction model trained exclusively on in-house data generated by the company's platform. Hermes is not a structural model and only predicts binding likelihood given an amino acid sequence and a Simplified Molecular Input Line Entry System (SMILES) representation of a small molecule. According to Leash, this model's simplicity enables speed and reports that the model is 200–500x faster than Boltz-2 with improved predictive performance when benchmarking against competitive AI models. Just two months later, Leash unveiled Artemis, a hit expansion tool that leverages Hermes to explore chemical space around a target of interest.

Researchers from Latent Labs develop generative AI models to design new antibodies, optimize existing enzymes, and advance genetic engineering.

Proteins from scratch

While small-molecule drugs continue to be the dominant modality in the drug discovery industry, many experts are eyeing the complexity of proteins to address their therapeutic problems of interest.

Simon Kohl, PhD, CEO of **Latent Labs**, is a former Google DeepMind researcher who was involved in the development of AlphaFold2, the 2024 Nobel Prize in Chemistry-winning algorithm for protein structure prediction, from start to finish. Kohl founded Latent Labs with the vision of building frontier models for biology, starting with designing proteins from scratch.

In July, Latent Labs released Latent-X, the company's first frontier model for *de novo* protein design. Latent-X achieved strong binding affinities in the picomolar range by testing only 30-100 candidates per target in wet lab experiments, offering an advance from traditional drug discovery pipelines, which require screening millions of random molecules for hit rates below one percent.

The designs from Latent-X focus on therapeutically relevant mini-binders and macrocycles. Binding affinities were reported to be competitive with the current state-of-the-art protein design models, RFdiffusion[3] and AlphaProteo,[4] in head-to-head experimental comparisons.

Kohl emphasizes that the model architecture, which jointly models sequence and structure at the all-atom level, makes Latent-X distinct.

"We've released movies where you can see the model make specific hydrogen bonds and pi stacking of aromatic rings. Generating biochemistry directly end-to-end allows us to make superior molecules from the start," said Kohl in an interview with *GEN*.

Latent-X is available as a web user

The Pursuit of an Optimal Diagnostic Strategy

From Single-Site to Global Scale: A Hybrid Future for CDx

Precision oncology is reshaping cancer care, with genomics increasingly guiding diagnosis and therapeutic decisions. At the heart of this transformation are companion diagnostics (CDx), essential tools to ensure patients receive the right treatment at the right time. However, despite remarkable scientific advances, pharmaceutical companies face a persistent challenge: how to bring precision therapies to market faster while ensuring efficiency, accuracy, and broad patient access?

To meet these demands, CDx pathways must evolve to align with regulatory requirements, offer short turnaround times (TAT) from development to commercialization, scale effectively, and guarantee equitable access worldwide.

The evolution of CDx development

The rise of biomarker-driven therapies created a need for more precise diagnostics making CDx an indispensable tool for identifying patients likely to respond to a treatment.

Historically, pharmaceutical companies have pursued two main CDx development and regulatory pathways: the single-site pre-market approval (ssPMA) and the distributed *in vitro* diagnostic (IVD) kit approaches.

The ssPMA model leverages a single laboratory to develop, validate, and perform analytical and clinical validation of the diagnostic test. Because it offers speed, flexibility, and reduced upfront investment, it is particularly valuable in early drug development when therapeutic efficacy is still being established. But its commercial reach is limited since testing is confined to one laboratory, limiting patient access.

In contrast, the distributed IVD kit model is designed for scale. Diagnostic manufacturers develop and validate kits ready for deployment across multiple laboratories worldwide, enabling broad patient access at therapeutic launch. The drawback is the higher cost and longer timelines required to align full IVD development with drug approvals.

Pharmaceutical companies often treat these models as mutually exclusive, yet both have strengths that can be combined to meet today's market needs.

Pioneering the future: A faster, broader, and smarter hybrid approach

The future of CDx development lies in a hybrid development and deployment model that combines centralized laboratory validation and clinical trial enrolment with decentralized testing at the point of care. By integrating ssPMA speed and IVD scalability, pharma companies can better align diagnostics with drug development timelines while ensuring broad access at launch.

By partnering with diagnostic companies, pharma can start the traditional central lab approach to develop the clinical trial assay (CTA), while the diagnostic partner simultaneously prepares the distributed IVD for decentralized testing. Through comparison or bridging studies, the ssPMA-approved assay can evolve into a globally distributed kit. This ensures alignment with drug development timelines and expands patient access from day one.

A strong example of this hybrid model is the partnership between SOPHiA GENETICS and Myriad Genetics[1] to develop MSK-ACCESS® powered with SOPHiA DDM™ into a CDx test. Combining the strengths of each, the companies will start by developing a CTA and pursuing FDA approval, which will later transition into an IVDR-certified, globally deployed kit via bridging studies. This unique CDx concept can be implemented across multiple platforms and laboratories, ensuring maximum patient access, including underserved regions.

What lies ahead?

The traditional pathways for CDx development no longer fulfil the scientific, clinical, and commercial needs of the industry. The future depends on collaboration between pharma and diagnostics companies to implement strategies that accelerate innovation, ensure regulatory alignment, and deliver local access at global scale.

As demonstrated by SOPHiA GENETICS and Myriad Genetics, the industry is moving toward smarter, more efficient, and collaborative solutions. Harnessing the strengths of a dual, centralized and decentralized approach allows pharma to combine efficiency, speed, and equity, redefining the future of CDx and expanding the reach of precision oncology worldwide. ■

Reference

1. Myriad Genetics and SOPHiA GENETICS to Develop an Innovative Companion Diagnostic Offering in Liquid Biopsy - SOPHiA GENETICS. 2025. Available from: https://www.sophiagenetics.com/news/myriad-genetics-and-sophia-genetics-to-develop-an-innovative-companion-diagnostic-offering-in-liquid-biopsy/.

interface that is accessible to researchers without a computational background. Kohl highlights that the premise for Latent Labs is to provide a resource to guide pharma companies and academic groups on the hardware and model needs for their protein design workflows.

"Making a technology accessible without the need for expert knowledge and AI infrastructure in this case is true democratization," emphasized Kohl.

Let's reprogram

From designing proteins not found in nature to extending healthy lifespan,

Joe Betts-LaCroix, PhD
CEO, Retro Biosciences

Retro Biosciences is applying AI models to advance cellular reprogramming for aging research. The company operates across different therapeutic modalities, from cell therapies to small molecules.

"We think of ourselves as a portfolio that invests in varying shots on goal toward that mission," Joe Betts-LaCroix, PhD, CEO of Retro, told *GEN*. "There are advantages and disadvantages to different modalities that are very complementary to each other, which makes it robust for Retro as a single company."

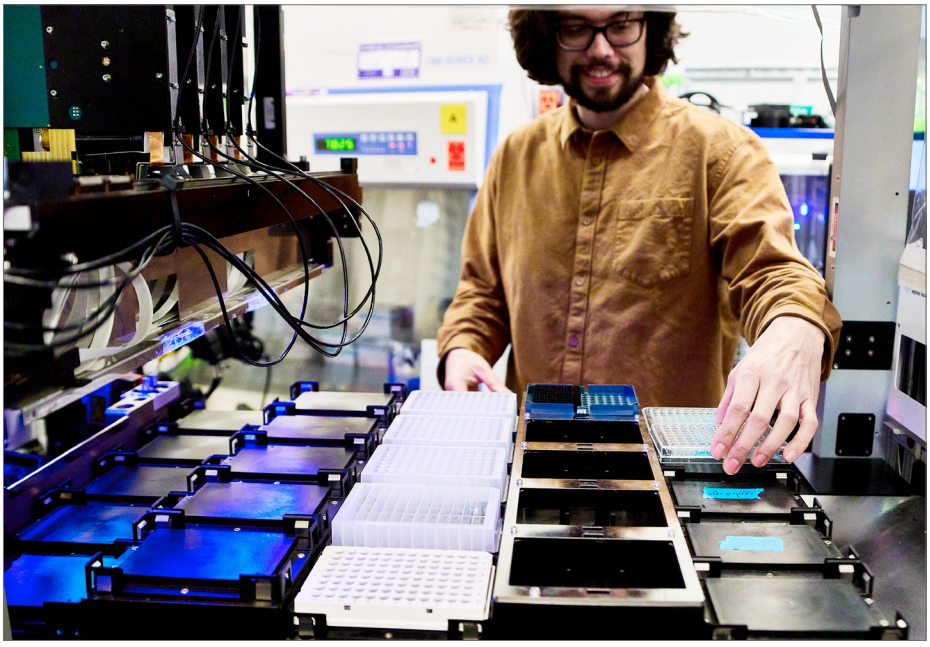
In a collaboration with **OpenAI** in August, Retro announced the design of enhanced variants of the Yamanaka factors, a set of four specific transcription factors (Oct4, Sox2, Klf4, and c-Myc) that can reprogram adult somatic cells into induced pluripotent stem cells (iPSCs), using GPT-4b micro, a miniature version of GPT-4o specialized for protein engineering. (GPT-4o is a flagship model from OpenAI that accepts input and produces outputs in the form of text, audio, image, and video.)

"Protein sequence and structure models learn patterns from raw data, but you can't prompt them based on what has been known in literature. In reprogramming, there's approximately 20 years of literature that you don't need to learn from scratch," said Rico Meinl, head of Applied AI at Retro, in an interview with *GEN*.

Proteins redesigned by GPT-4b micro achieved greater than a 50-fold higher expression of stem cell reprogramming markers than wild-type controls *in vitro* and demonstrated enhanced DNA-damage-repair capabilities, indicating improved rejuvenation potential.

The model incorporates protein information in the form of textual descriptions, including co-evolutionary homologous sequences, and protein interaction networks, which allows GPT-4b micro to be prompted to generate new sequences with designed properties. As most of the data is structure-free, the model is adaptable to both structured proteins and proteins with intrinsically disordered regions, including Yamanaka factors whose activity depends on transient interactions with diverse binding partners.

From predicting small molecule binding affinity to cellular reprogramming, large-scale biological data combined with new model architectures continue to propel the AI revolution forward. Time will tell if rising computational power will lift the boat of therapeutic potential. GEN



Using a liquid-handling robot, a Retro Biosciences scientist develops automation protocols to accelerate laboratory workflows. Automated screening helps the company identify cellular interventions targeting aging mechanisms.

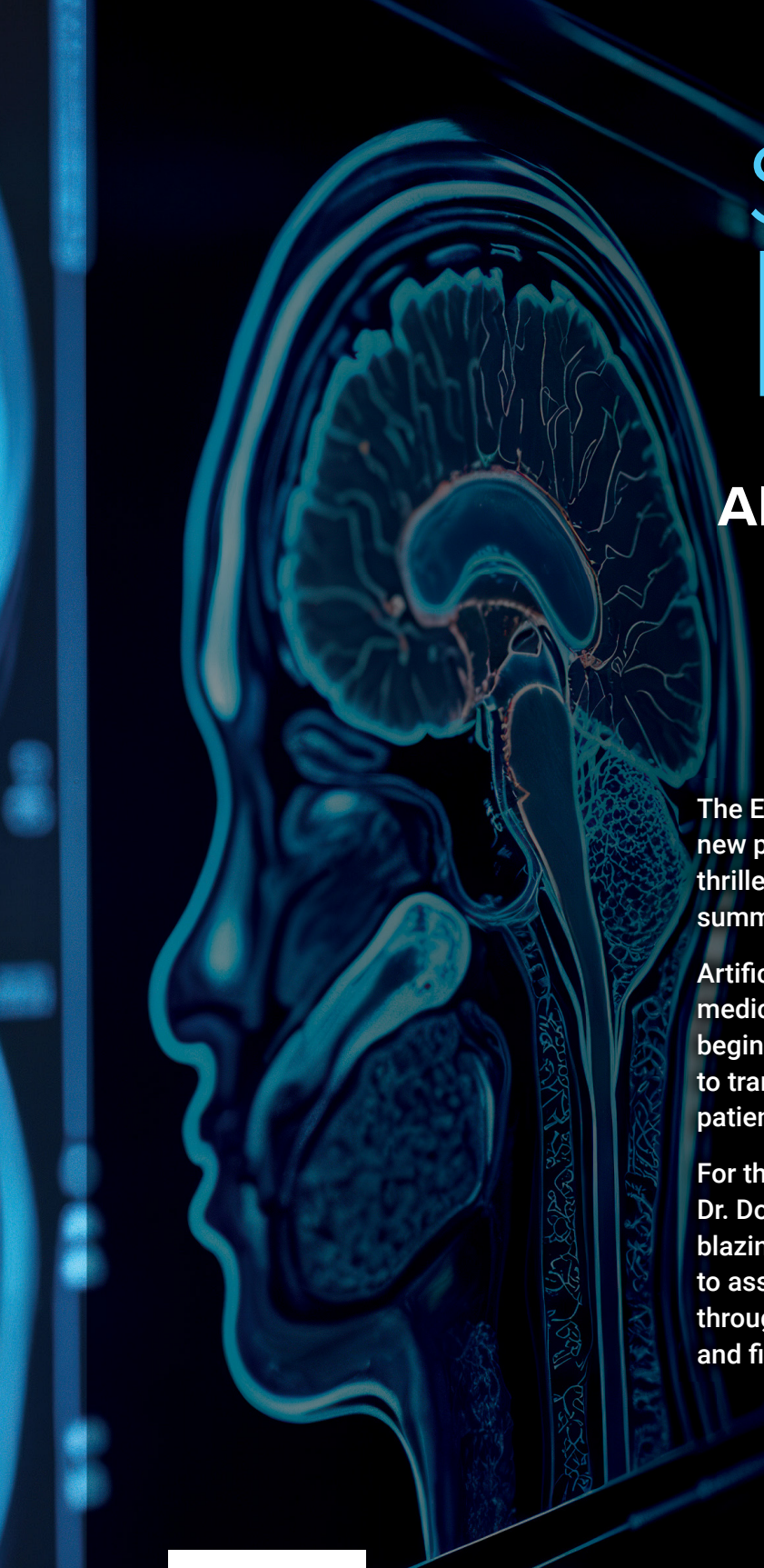
References

1. Abramson J, Adler J, Dunger J, et al. Accurate structure prediction of biomolecular interactions with AlphaFold 3. *Nature.* 2024; doi: 10.1038/s41586-024-07487-w.

2. Krishna R, Wang J, Ahern W, et al. Generalized biomolecular modeling and design with RoseTTAFold All-Atom. *Science.* 2025;384(6693):eadl2528; doi: 10.1126/science.adl2528.

3. Watson JL, Juergens D, Bennett NR, et al. De novo design of protein structure and function with RFdiffusion. *Nature.* 2023;620(7976):1089–1100; doi: 10.1038/s41586-023-06415-8.

4. Zambaldi V, La D, Chu AE, et al. De novo design of high-affinity protein binders with AlphaProteo. *arXiv.* 2024; doi: https://arxiv.org/abs/2409.08022



SAVE THE DATE

3rd Annual AI in Precision Oncology Virtual Summit!

DECEMBER 16, 2025
11 AM–3:00 PM ET

The Editors of ***AI in Precision Oncology***, the groundbreaking new peer-review journal from Mary Ann Liebert, Inc. are thrilled to welcome you to the Journal's third annual virtual summit: The State of AI in Precision Oncology.

Artificial Intelligence (AI) is rapidly changing the practice of medicine in general and oncology in particular. Clinicians are beginning to deploy a range of AI applications and strategies to transform their practice, personalize treatments and save patient lives.

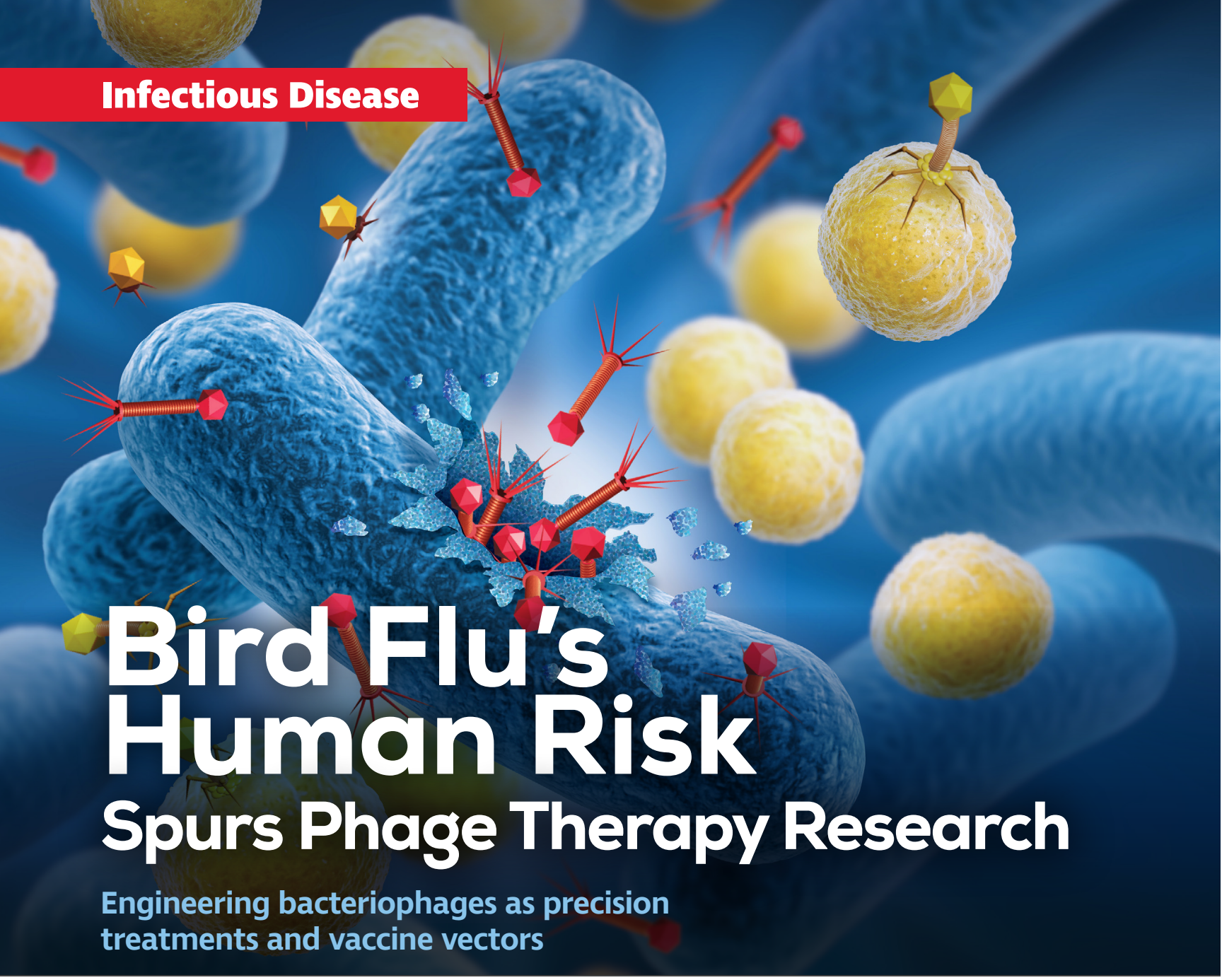
For this 2025 virtual summit, Founding Editor-in-Chief Dr. Doug Flora and colleagues have invited a group of trail-blazing physicians, oncologists, and AI thought leaders to assess the state of AI in the field of precision oncology through a series of keynote presentations, panel discussions, and fireside chats.

MORE INFORMATION AND AGENDA TO FOLLOW!

SCAN HERE TO REGISTER FOR FREE

HOSTED BY

AI IN PRECISION ONCOLOGY



Bird Flu's Human Risk Spurs Phage Therapy Research

Engineering bacteriophages as precision treatments and vaccine vectors

By Kathy Liszewski

Highly pathogenic avian influenza A (H5N1, commonly known as HPAI or bird flu) is a formidable worldwide public health concern. With approximately a 100% mortality rate, the World Organization for Animal Health estimates that more than 633 million birds (poultry and wild birds) have been lost globally over the past 20 years. The U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) estimates that from 2022 (origin date of present outbreak) to April 2025, more than 168 million birds have died, primarily via culling ("depopulation on detection"). Cases are occurring in all 50 U.S. states.

Further, spillovers into other species, such as dairy cows, domestic animals, and even marine mammals, are increasing. For example, by September 15, 2025, bird flu had affected over 1,790 dairy herds across 18 states, according to the Center for Infectious Disease Research and Policy.

Although rare, human spillovers are also occurring primarily from direct exposure to infected animals. A recent report by the U.S. Centers for Disease Control and Prevention (CDC) determined that between March 2024 and May 2025, 70 cases of humans infected with HPAI were documented in

Above. Bacteriophages can precisely target and destroy harmful pathogenic bacteria such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Scientists at Armata Pharmaceuticals utilize tools such as synthetic biology to engineer therapeutic improvements into both phages and manufacturing hosts.

the U.S., with one death.

While bird flu primarily devastates avian populations, its occasional spillover into humans raises concern, not only because of the viral infection itself, but also due to the secondary bacterial infections that often complicate severe influenza cases. This intersection of viral and bacterial disease has renewed attention on bacteriophage therapy—not only as a precision tool to combat opportunistic bacterial pathogens, but also as an innovative platform to develop vaccines against HPAI itself.

Bacteriophages, or phages for short, are viruses that target and destroy bacteria with remarkable specificity. They consist of genetic material encased in a protein shell that can attach to bacterial cells. Some phages replicate by lysing their hosts, while others integrate into bacterial genomes or persist without lysis, thereby eliciting immune responses from the bacterial host.

In this article, we feature insights from the CDC on the current state of the bird flu epidemic alongside perspectives from companies advancing phage therapeutics as versatile tools for combating resistant bacterial strains and for developing effective, scalable vaccines against viral diseases.

CDC perspective

Gabriel Alvarado, public affairs specialist at the CDC, warns, "Because most people don't have pre-existing immunity to avian influenza viruses, these viruses have the potential to cause a flu pandemic in people if they were to gain the ability to more easily infect and spread efficiently between people."

Alvarado says that a recent CDC scientific report made an assessment of the potential pandemic risk of two viruses from human cases and concluded that the risk for this group of viruses is considered moderate. "That assessment validates the value of a continued proactive, coordinated U.S. government response, including continued surveillance and reporting and investigation of every human infection from avian influenza A viruses."

Phage as vaccine vectors

Amid escalating concerns over avian influenza, the development of vaccine platforms that can be rapidly adapted and scaled has become a priority.

In addition to targeting antimicrobial resistance, **Cytophage Technologies** also is developing phage-based vaccines against H5N1 using a filamentous phage vector that displays viral epitopes.

"Unlike typical lytic phages, which destroy their bacterial hosts and produce only a short burst of particles, these filamentous phages are extruded continuously," explains Steven Theriault, PhD, CEO. "The bacteria essentially become miniature phage factories, producing a steady stream of vaccine particles that stimulate the immune system. In this system, we have longevity on our side."

Theriault believes the key to leveraging phage-based vaccines lies in engineering phage DNA to express antigenic epitopes on the phage surface, with the critical challenge being the selection of stable epitopes. "Viral epitopes can change. To overcome this, we study how the viral shifts occur and carefully select epitopes less likely to be altered by natural evolution."

According to Theriault, phages as vaccine vectors may offer important advantages. They are self-adjuvanting, strengthening the immune response and reducing or even eliminating the need for booster shots. Manufacturing is also highly efficient—Cytophage estimates it can produce about 150 million doses in seven days. Unlike many existing vaccines, phage-based products can be stored at room temperature, simplifying global distribution. Safety is another key advantage: phages are non-toxic, do not infect human or animal cells, and cannot revert to pathogenic forms.

Theriault says that, unlike other vaccines, phages do not integrate into the host genome, which mitigates risks linked to genomic integration. He also notes that another strength is the speed at which phages can be adapted. "In contrast to the several months required to retool mRNA vaccines, phages can be modified in just a few days. This

Bacteriophage technologies are being leveraged to create vaccines against avian influenza (bird flu) at Cytophage Therapeutics. Steven Theriault, PhD, CEO, working in the laboratory. [Cytophage Therapeutics]

rapid turnaround could prove decisive in responding to evolving outbreaks like H5N1."

Dual-action phages

Severe viral infections, such as bird flu, often lead to secondary bacterial infections, particularly in hospitalized or immunocompromised patients. By targeting the specific bacteria responsible, phage therapy could play a crucial role in treating infections, such as bacterial pneumonia. This approach could allow for more tailored and potentially more effective treatments compared to traditional antibiotics, which are often broad-spectrum and face increasing resistance issues.

Deborah Birx, MD CEO, Armata Pharmaceuticals

Sebastien Lemire, PhD, Dir., Discovery and Engineering, Armata Pharmaceuticals

"Phage-based therapies represent a paradigm shift because, unlike static antibiotics, phages are living biologics that can be thought of as 'trainable' antibiotics as they have co-evolved alongside bacteria for billions of years," notes Amanda Burkardt, CEO, **PHIOGEN**.

Burkardt says PHIOGEN is developing novel "dual-action" phages that not only fight bacterial infections but also reduce or eliminate recurrences. She reports, "While most phage companies intentionally avoid immune-stimulating phages to reduce the risk of neutralizing antibodies if retreatment is needed, we take the opposite approach; selecting phages that strongly activate the immune system against the infecting pathogen, so patients are, in effect, immunized and protected against future infections without repeated dosing."

The company's proprietary technology platform combines directed evolution, high-throughput screening, and immune-relevant models to identify and train phages with enhanced antibacterial and immunogenic properties. Burkardt elaborates, "This is built directly into our technology platform to select for rare phages that both stimulate immunity and remain potent bacterial killers. By systematically harnessing the natural adaptability, we are uncovering entirely new functionalities of phages that antibiotics cannot provide."

Both of PHIOGEN's lead candidates emerged directly from this platform. PHI-UI-01, targets recurrent urinary tract infections caused by resistant *Escherichia coli*, while a parallel program's candidate, PHI-BI-01, takes aim at extraintestinal pathogenic *E. coli* (ExPEC). Burkardt discloses, "Our ExPEC bacteremia program is supported by a recent CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator) award and is focused on addressing life-threatening bloodstream infections and delineating the mechanism behind this novel therapeutic and preventative effect. Both programs are based on the same principle of combining immediate bacterial clearance with long-term protection, ensuring a pipeline that addresses both high-prevalence and high-mortality conditions."

This technology could also help address the pandemic potential of diseases such as bird flu spreading to humans. Burkardt comments, "Our platform is highly relevant to the secondary drug-resistant bacterial infections, like sepsis, that often complicate severe viral illnesses and drive poor outcomes in vulnerable patients. Our dual-action therapeutics offer a two-fold benefit in this setting: (1) immediate treatment of life-threatening bacterial co-infections and (2) reduction in the risk of recurrence or reinfection during prolonged illness or recovery."

Burkardt concludes, "Our ultimate goal is to build a pipeline of safe, scalable products that not only address today's resistant and chronic infections but also anticipate tomorrow's emerging threats."

PHIOGEN scientists are pioneering a new approach to phage therapy by developing first-in-class 'dual-action' phages that both eliminate drug-resistant bacteria and train the immune system to prevent future reinfections. [PHIOGEN]

Phage cocktails

Armata Pharmaceuticals is developing high-purity, pathogen-specific bacteriophage therapeutics to treat antibiotic-resistant and difficult-to-treat bacterial infections, initially focusing on *Staphylococcus aureus* (systemic infections) and *Pseudomonas aeruginosa* (respiratory infections). "Phages are the most ubiquitous organisms on earth," proffers Sebastien Lemire, PhD, director of Discovery and Engineering. He continues, "Phages are highly species-specific, with a mechanism of action distinct from broad-spectrum antibiotics, that enables phages to bind to and kill specific targeted bacteria while uniquely preserving the normal, healthy human microbiome."

Armata is developing fixed multi-phage cocktails targeting the desired pathogens. The company utilizes synthetic biology to engineer both phages and manufacturing hosts for improved pharmacological properties. They also employ next-generation sequencing to characterize large proprietary phage libraries.

Lemire elaborates, "Advantages of producing multi-phage cocktails include improved activity against a broad range of clinical isolates and increased genotypic and phenotypic diversity to minimize resistance development."

Armata has completed three Phase II clinical trials utilizing two distinct phage cocktails, AP-PA02 and AP-SA02, targeting *P. aeruginosa* and *S. aureus*, respectively. Deborah Birx, MD, CEO, says that *S. aureus* plays an especially important role in many secondary post-viral infections. "What we have been able to demonstrate using AP-SA02 in our recent Phase II diSArm clinical trial is that our phages injected intravenously can home in to the site of infection, penetrate biofilms, infect, and lyse *S. aureus*. Many deaths post flu, and most likely also potentially from avian flu, are due to bacterial pneumonia and could be treated with phages, as we have shown in complicated bacteremia patients."

Amanda Burkardt
CEO, PHIOGEN

Jonathan Solomon, PhD
CEO, BiomX

Big data and AI meet wet lab

"Phage therapeutics come with unique challenges," advises Jonathan Solomon, CEO, **BiomX**. He continues, "Selecting the right phages requires broad libraries and deep screening, since no single phage works against all clinical bacterial strains. Engineering the phage adds complexity but also opportunity. We need to ensure modifications improve potency, host range, and resistance-avoidance."

BiomX is addressing those challenges with its BOLT (BacteriOphage Lead to Treatment) platform and in-house expertise. Solomon elaborates, "Our BOLT platform is designed to systematically identify and optimize phage therapies against specific bacterial targets. It works by starting with one of the world's largest proprietary collections of natural phages, which we screen against thousands of clinical bacterial isolates to identify the most active candidates. We then apply advanced computational and AI tools to predict and evolve phages with improved potency, host range, and the ability to overcome bacterial defense systems."

Next, the company combines complementary phages into optimized cocktails, balancing lytic activity, biofilm penetration, and resistance prevention to create their targeted therapies. "This integrated approach, where big data and AI meet wet-lab validation, is what enables us to design scalable, highly precise potential phage treatments for some of the most problematic pathogenic bacteria," says Solomon.

BiomX is advancing its phage therapies in clinical trials against *P. aeruginosa* and *S. aureus*. Solomon projects, "What makes these programs especially potentially powerful is that each target represents a 'pipeline in a product.' Because these same pathogenic bacteria drive disease across multiple conditions, our validated phage cocktails have the potential to expand into many patient populations."

And as for bird flu, Solomon says, "Bacteriophages have been at war with bacteria for millions of years, constantly adapting to eradicate them. The bacteria that drive severe secondary infections in bird flu are no exception—there are already phages and phage cocktails with proven activity against these pathogens. In a pandemic-like scenario, where secondary bacterial infections can be deadly, this ability to quickly bring a targeted, validated therapy to market could make phage therapy a uniquely powerful solution." GEN

Through its BOLT platform, BiomX integrates artificial intelligence, validated by experimental microbiology, to create phage therapies aimed at eliminating harmful bacteria linked to chronic diseases. [BiomX]

Bioprocessing

Beyond Process Development: AI Reshaping Use of Digital Twins

Artificial intelligence is changing how biopharma creates and uses digital models of manufacturing processes

By Gareth Macdonald

In industrial engineering, digital twins—computer models of systems or processes—let scientists try out ideas before finalizing designs. In addition, on the factory floor, twins can model processes in real-time, enabling automated control.

Initially, the most common use of digital twins in biopharma was for process development. Engineers would use a combination of historical and experimental data as well as sound scientific principles to model, test, and then fine-tune unit operations.

Process development is still a major focus, but in recent years digital twins have started to be employed more widely, according to Zachary Sample, an enterprise consultant at industrial engineering firm, **Emerson**.

"Digital twin technologies can bring value across the entire biopharmaceutical development chain, leading to faster time to market. As a result, we are seeing digital twins implemented at every stage of the pipeline.

"In process development," Sample continued, "digital twins can help teams improve their understanding of the process and drive predictability across the entire development stage. Teams can use digital twins to unlock rapid prototyping, reduce the overall number of experiments necessary to define the process, and define the specific parameters to provide an optimized process."

Digital twins have multiple uses in commercial manufacturing as well, Sample says. "Digital twins provide an ideal platform for training and testing, to drive operational excellence. A robust simulation platform facilitates the movement toward more autonomous operations, improves performance predictions, drives predictive reliability, and ensures product quality."

Sample cited a recent customer project Emerson worked on as an example, explaining, "Simulation software was able to help the team improve processes and product purity.

"Through rigorous testing via process models, the team was able to reduce impurity levels from hundreds of parts per million (ppm) to 20 ppm. They also reduced crystallization time from eight hours to 20 minutes."

Another customer used Emerson's digital twin technology to optimize a spray drying process. "Experimentation was costly, so they needed a more efficient and cost-effective way to assess process variations.

"Using simulation software, the team was able to employ experimental data to test, dramatically reducing the cost of experimentation to reach the target," Sample said.

Digital future

Digital twins are already well-established in biopharma, and companies continue to test new uses, according to Alexander Seyf, CEO of U.K.-based industrial "smart technology" developer, **Autolomous**.

"We see some truly fascinating appli-

Above. Digital twins are helping engineers to develop and optimize biopharmaceutical manufacturing processes before they are moved into the production facility. The efficiency gains and increased yields more than offset the initial costs researchers say. [SweetBunFactory/iStock/Getty Images Plus]

cations beyond simple process optimization. Some companies are using digital twins to create "soft sensors," which are virtual models that estimate hard-to-measure attributes like nutrient levels or viral vector titer in real-time. This enables more flexible process control.

"Another significant use is in tech transfer and scale-up, where a twin can simulate the shift from a small lab-scale process to a full-scale manufacturing run, significantly lowering risk and time to market," he said.

This is in keeping with the approach taken by **GSK**, which is using 54 digital twin models across 12 drug products to simulate processes, anticipate issues, and accelerate manufacturing.

GSK has also used digital twins during technology transfer to third-party contractors, manufacturing scale-up, and product launches. Twins have also informed the firm's manufacturing equipment selection for various infectious disease and HIV-related projects.

In addition, for one vaccine, a digital twin helped GSK optimize the processes and unlock capacity to produce an extra million doses.

Already well-established in the process development lab, digital twins are increasingly being used on the factory floor to monitor and automate the control of biopharmaceutical manufacturing operations. The ability to use process data to build models that provide feedback in real-time also helps improve quality control processes. [primeimages/Getty Images]

AI revolution

The biopharmaceutical industry's use of digital twins is only likely to become more diverse, according to Sample, who says advances in AI will be a major catalyst.

"Historically, digital twins have required significant effort for implementation. That is changing dramatically as automation suppliers have begun building AI capabilities into the software," he said. "Today, instead of needing many process engineers to spend months of time to perform the modeling, AI tools reduce the barrier for configuration."

And, Sample says, soon AI will be able to make models—digital twins—automatically.

"If we feed an AI tool with chromatography skid data with the source information, the AI tool can understand what that means from a first principles standpoint. It knows what a chromatography skid is and can build a model from that data."

"We can use AI to build deterministic models and then also use that same AI to perform hybrid modeling—which is especially helpful where the modeling strategy is unclear and we do not have the mechanistic models to bridge the gap with empirical models.

"Ultimately," Sample continued, "AI advances are leading to a future where digital twins are both more robust and simultaneously easier to develop and deploy."

This view is shared by Daniel Espinoza from the faculty of engineering at Lund University in Sweden, who points to the additional computational power provided by AI systems as the key dynamic.

"The mechanistic digital model has been well studied and documented over the past 20 years, and the techniques and groundwork for real-time digital shadows and digital twins already exist.

"The way to drive progress forward in their application in industry lies in solving the fundamental issues of computational cost and data availability. The latter requires innovation in online sensor technologies, while the former can be solved in two ways: by improving the simulation speed by means of parallelization or more efficient solver algorithms, or by replacing the mechanistic digital model with a fully data-driven or hybrid approach," he said.

But the impact AI has on digital twins—and process modeling in general—may be even more profound according to Espinoza, who suggests that, with enough data, such systems could even replace traditional approaches.

"Artificial neural networks (ANNs) have been showcased as candidates for so-called surrogate models, replacing the mechanistic model entirely and achieving similar performance with much faster computation speeds.

"A downside to these is that the amount of data required to train them is much greater than for mechanistic models, requiring either much more experimentation time and resources, or an already-trained mechanistic model to

generate training data," he said. "Hybrid approaches, such as physics-informed neural networks (PINNs), bypass the data requirement by including a mechanistic constraint to the neural network."

Seyf also expects that AI will come to redefine how biopharma uses digital twins.

"The evolution of digital twins in biopharma will be characterized by more integration and autonomy. We expect twins to become even more advanced, transitioning from focusing on a single process or asset to a "digital thread" that covers the entire product lifecycle—from R&D to manufacturing and supply chain logistics.

"AI and automation will drive this change. AI could eventually make twins self-optimizing, allowing them to adjust and predict in real-time to maintain optimal conditions and prevent failures without human oversight," he said. "This move towards autonomous manufacturing will greatly enhance efficiency, quality, and compliance, ultimately speeding up the delivery of life-saving therapies to patients." GEN

Point of View

Continued from page 21

industrial biotechnology. These various readiness frameworks can transform partnership negotiations from subjective assessments to data-driven milestone structures.

Additionally, the National Biotechnology and Biomanufacturing Initiative has committed $2 billion to ensure "we can make in the United States all that we invent in the United States." Yet without robust private sector engagement through partnership models like BIBs, this vision remains unrealized. To maximize BIB partnerships' potential, federal policymakers should consider three proven incentive frameworks—the CHIPS Act, tax deferrals and capital gains exclusions in designated Opportunity Zones, and permanent R&D tax credits—to create a new model of public-private partnerships (PPPs). These incentive frameworks leverage proven bipartisan models, and mirroring them can create comprehensive benefits for investment in biomanufacturing facilities and equipment, workforce development, innovation, and R&D that make corporate participation in BIB partnerships highly profitable.

Lastly, the emerging policy landscape supports expanded corporate-startup partnerships. The National Biotechnology and Biomanufacturing Initiative's call for a National Biotechnology Coordination Office would provide centralized coordination across multiple agencies, while proposed Independence Investment Funds could provide non-dilutive risk capital for early-stage ventures. Organizations like BioMADE have already shown how this vision can be operationalized through milestone-based grants and infrastructure co-development. Through cost-sharing and milestone-oriented funding, BioMADE has fostered the development of nine new bioindustrial projects, including waste-to-bioproducts, natural rubber from dandelions, and scalable purification processes, demonstrating that government grants can mirror BIBs' logic without prescribing the science. These initiatives create the regulatory clarity and financial foundation necessary for large-scale corporate engagement in BIB structures.

Despite current budget challenges, American leadership in artificial intelligence, biotechnology, and augmenting our workforce is a bipartisan issue, because they are national security issues. Senators Todd Young (R-IN) and Alex Padilla (D-CA) are leading the legislative groundwork with six key bills. The proposed Foundation for Enabling Biotechnology Innovation Act aims to "foster public-private partnerships" and "accelerate U.S. biotechnology commercialization," while the NSCEB-endorsed report explicitly calls for making "biomanufacturing scale-up predictable, rapid, and cost-competitive" through federal investment. These efforts, though nascent, show that political will is aligning around incentive structures to support a model such as BIBs.

Making BIBs a reality

The timing couldn't be better. America's entrepreneurial advantage lies in our boldness and willingness to innovate with new ways of doing business. While other countries may have government-directed industrial policies, the U.S. excels at creating novel partnership structures that align private sector incentives. BIBs represent exactly this kind of American innovation: a market-driven solution that leverages our unique combination of entrepreneurial startups and industrial expertise.

Corporate leaders, biotech startups, investors, industry participants, and federal policymakers all have a role to play in seizing the opportunity to own America's bio-industrial leadership. BIBs offer a roadmap, but what remains is the will to act. The companies and policymakers that recognize this moment and commit to systematic BIB development will shape the next chapter of American manufacturing. The bioeconomy revolution is not inevitable—it requires deliberate choices and sustained commitment through new models of public-private collaboration. ■

Henry Lee, PhD, is the CEO of Cultivarium.

Combining Ligand- and Structure-Based Methods

for More Effective Virtual Screening

Optibrium's dual approach yields gains in efficiency and confidence in results

By Tamsin Mansley, PhD

Tamsin Mansley, PhD
President and Global Head of Application Science, Optibrium

In drug discovery, virtual screening is a fast and cost-effective way of narrowing down vast chemical libraries to identify the most promising hits, reducing synthesis and testing requirements while improving research efficiency.

Virtual screening serves two distinct purposes:

- Library enrichment, where very large numbers of diverse compounds are screened to identify a subset with a higher proportion of actives.
- Compound design, involving detailed analysis of smaller series to guide optimization. Here, the focus shifts to greater precision and ideally quantitative prediction of binding affinity.

Advances in computational power and data availability have enhanced the performance and efficiency of these methods, increasing their adoption and furthering their impact in discovery workflows.

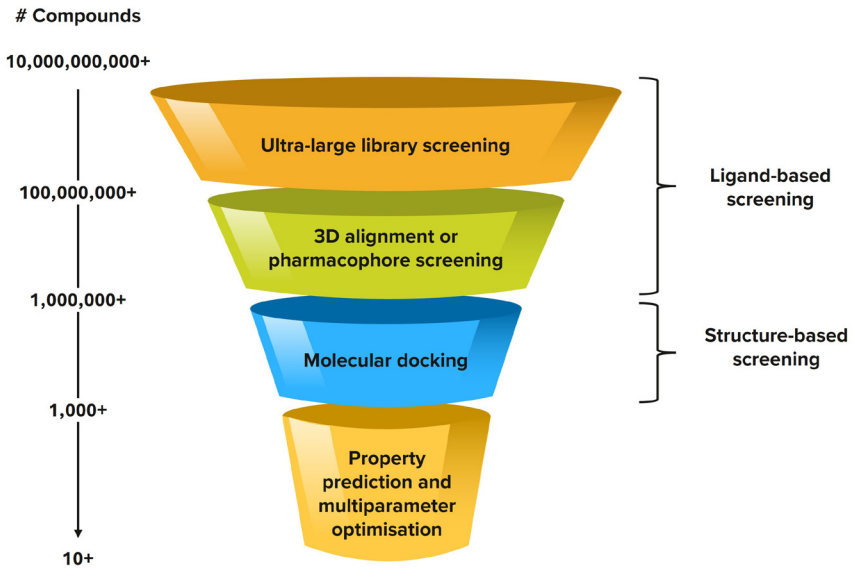


Figure 1. Illustrative example of how ligand and structure-based screening methods can be combined to identify the most promising hits from vast chemical libraries.

Comparing virtual screening methods

Virtual screening methods fall broadly into two categories: ligand- and structure-based.

Ligand-based virtual screening doesn't require a target protein structure, Instead, it leverages known active ligands to identify hits that show similar structural or pharmacophoric features.

These approaches offer faster and cheaper computation than structure-based methods, excelling at pattern recognition and generalization across diverse chemistries. They can be particularly valuable during the early stages of discovery for prioritizing larger chemical libraries and when

no protein structure is available.

At the broadest scale, methods including infiniSee™ (by BioSolveIT) and exaScreen (by Pharmacelera) enable efficient screening of ultra-large synthetically accessible chemical spaces containing tens of billions of compounds. These technologies assess pharmacophoric similarities between library compounds and known active ligands, identifying the potential to form certain types of interactions, but trade off speed in exploring these vast spaces with sensitivity and precision.

For screening smaller libraries (up to thousands or even millions of compounds), other ligand-based methods focus on detailed conformational analysis of individual compounds. Though generally slower and more computationally expensive, they deliver more accurate results. These methods align known active ligands by superimposing 3D structures to maximize similarity across pharmacophoric features, such as shape, electrostatics, and hydrogen bonding interactions. This creates a binding hypothesis to quantify how well virtual compounds align. Traditional pharmacophore methods require users to specify alignment features, whilst modern approaches like eSim™ (by Optibrium), ROCS®, (by OpenEye Scientific) and FieldAlign (by Cresset) automatically identify relevant similarity criteria with which to rank potentially active compounds.

Advanced methods like Quantitative Surface-field Analysis (QuanSA™),[1] (by Optibrium) take this approach further by constructing physically interpretable binding-site models based on ligand structure and affinity data using multiple-instance machine learning. Importantly, most 3D ligand-based methods only provide ranking scores for library enrichment, but 3D quantitative structure-activity relationship methods like QuanSA can predict both ligand binding pose and quantitative affinity, even across chemically diverse compounds. This provides more resolution in predictions with which to guide the efficient design of highly active compounds.

Structure-based virtual screening uses target protein structural information, typically obtained experimentally through X-ray crystallography or cryo-electron microscopy, or through computational methods such as homology modeling.

Structure-based methods provide insights into atomic-level interactions, including hydrogen bonds and hydrophobic contacts. They often provide better enrichment for virtual libraries by incorporating explicit information about the shape and volume of the binding pocket.

The most common approaches involve docking compounds into known binding pockets. Numerous docking methods excel at placing ligands into binding sites in reasonable orientations, but the challenge lies in scoring and ranking the poses. Typically, they cannot accurately predict binding affinities but can eliminate compounds that won't fit into the binding pocket, thereby increasing the enrichment of high-ranked compounds.

Moving beyond docking, Free Energy Perturbation (FEP)[1] calculations represent state-of-the-art structure-based affinity prediction. Though accurate, they are computationally very demanding and typically limited to small structural modifications around known reference compounds.

The impact of AlphaFold

AlphaFold (by Google DeepMind) has significantly expanded the availability of protein structures. However, important quality considerations remain about their reliability in docking performance.

Models typically predict a single static conformation, potentially missing conformational differences associated with ligand binding. This can yield false negatives or inaccurate binding pose predictions.[2] Additionally, while AlphaFold's backbone predictions are reliable, it can struggle with side chain positioning, which is critical to achieving good docking results. Without careful post-modeling refinement, AlphaFold has so far shown limited success in naïve docking experiments.

Co-folding methods that generate ligand-bound protein structures, like Boltz-2 (by MIT and Recursion) and AlphaFold 3, have recently become available. Despite their promise, questions remain about their generalizability. Performance has been shown to falter

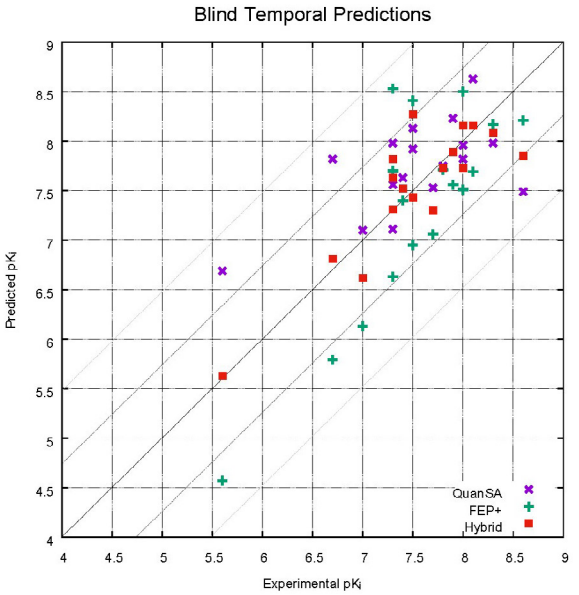


Figure 2. A Comparison of activity predictions for a 17-molecule subset of potential LFA-1 inhibitor molecules using QuanSA (MUE = 0.44), FEP+ (MUE = 0.56), and a hybrid method (MUE = 0.25). Taken from Cleves et al 2021 (CC-BY-NC-ND 4.0) (1)

when predicting structures that differ from the training set[3] or when predicting allosteric binding sites.[4] Though their utility has been limited, they can still serve as valuable ways to develop experimental hypotheses.

The power of a hybrid approach

Structure- and ligand-based approaches are highly complementary, often yielding more reliable results when used together.

Sequential integration first employs rapid ligand-based filtering of large compound libraries, followed by structure-based refinement of the most promising subset. For example, an initial ligand-based screen can identify novel scaffolds early, offering chemically diverse starting points that can then be analyzed through docking experiments to confirm binding interactions.

This approach conserves computationally expensive calculations to only a small set of compounds likely to succeed, increasing efficiency while improving precision over using a single method.

Parallel screening involves running both ligand- and structure-based screening independently but simultaneously on the same compound library. Each method generates its own ranking of compounds, and results can be compared or combined using consensus scoring frameworks.

• Parallel scoring selects top candidates from both approaches without requiring consensus. This increases the likelihood of recovering potential actives and helps mitigate the limitations inherent in each approach.

• Hybrid (consensus) scoring creates a single unified ranking through multiplicative or averaging strategies. By favoring compounds ranking highly across both methods, this approach reduces the number of candidates while increasing confidence in selecting true positives.

The choice between strategies depends on your objectives: use parallel approaches for broader hit identification and preventing any missed opportunities when you can afford to test more compounds, and consensus methods when you need higher confidence in your selections.

Case study

In collaboration with Bristol Myers Squibb, we found improved affinity prediction in LFA-1 inhibitor lead optimization.

Compounds in this work[1] were generated to identify orally available small molecules targeting the LFA-1/ICAM-1 interaction, which modulates immune responses. Structure-activity data from these compounds were split into chronological training and test datasets for QuanSA (ligand-based) and FEP+ (structure-based), (by Schrödinger) affinity predictions.

Each individual method showed similar levels of high accuracy in predicting pKi. However, the hybrid model averaging predictions from both approaches performed better than either method alone. Through partial cancellation of errors, the mean unsigned error (MUE) dropped significantly, achieving high correlation between experimental and predicted affinities.

Progressing virtual screening results

Binding affinity alone does not make a promising therapeutic candidate. Multi-parameter optimization (MPO)[5] helps to prioritize hits from virtual screening by identifying compounds with the best overall drug-like properties and the highest probability of clinical success. MPO methods incorporate multiple objectives, including potency, selectivity, ADME, and safety profiles.

Summary

Your virtual screening strategy will depend on your success criteria, the computational time and resources you are willing to invest, and the available data. Ligand-based methods provide a faster and less costly alternative, valuable for filtering very large, chemically diverse libraries, or when structural data is limited. Structure-based approaches work when high-quality protein structures are available. They often provide better library enrichment but are more computationally expensive.

Evidence strongly supports hybrid approaches that combine atomic-level insights from structure-based methods with pattern recognition capabilities of ligand-based approaches. Whether through sequential workflows or parallel consensus scoring, integrated strategies can outperform individual methods by reducing prediction errors and increasing hit identification confidence.

Tamsin Mansley, PhD, is the president of Optibrium Inc. and global head of application science.

References

1. Cleves, A. E., Johnson, S. R. & Jain, A. N. Synergy and Complementarity between Focused Machine Learning and Physics-Based Simulation in Affinity Prediction. *J. Chem. Inf. Model.* 2021; 61, 5948–5966.

2. Scardino, V., Di Filippo, J. I. & Cavasotto, C. N. How good are AlphaFold models for docking-based virtual screening? *iScience.* 2023; 26, 105920.

3. Škrinjar, P., Eberhardt, J., Durairaj, J. & Schwede, T. Have protein-ligand co-folding methods moved beyond memorisation? *bioRxiv* preprint 2025;https://doi.org/10.1101/2025.02.03.636309.

4. Nittinger, E., Yoluk, Ö., Tibo, A., Olanders, G. & Tyrchan, C. Co-folding, the future of docking – prediction of allosteric and orthosteric ligands. *Artif. Intell. Life Sci.* 2025; 8, 100136.

5. Segall, M. D. Multi-Parameter Optimization: Identifying High Quality Compounds with a Balance of Properties. *Curr. Pharm. Des.* 2012;18, 1292–1310.

Targeting Ice Recrystallization to Improve Cryopreservation Consistency

BioLife incorporates ice recrystallization inhibitors (IRIs) into cryopreservation workflows and reduces recrystallization-driven injury and variability

By Rebecca Mercier, PhD, Ana Clementin, PhD, Jason Acker, PhD, and Robert N. Ben, PhD

Biopreservation is a process by which the degradation of biologics is suppressed to enable the recovery of structure, viability, and function. Cryopreservation is the most common method for long-term biopreservation, using temperatures lower than 0 °C, generally ranging between -80 °C and -196 °C. At ultra-low temperatures, biochemical activity is effectively suspended, allowing materials to be preserved for extended periods without degradation or loss of function. This technology is essential across a range of sectors, including cell and gene therapy, regenerative medicine, biomanufacturing, precision agriculture, and biodiversity conservation.

Understanding how freezing imposes physical and chemical stress on biological systems was foundational to the development of modern cryobiology. Ice formation and solute imbalance were identified as two primary drivers of cryoinjury due to their ability to induce membrane rupture, osmotic shock, and intracellular damage.

To mitigate these effects, cryoprotective agents (CPAs) were discovered and developed based on their ability to reduce ice formation, regulate osmotic stress, and stabilize cellular structures. Small molecules such as glycerol and dimethyl sulfoxide (DMSO) became widely adopted due to their ability to permeate cells and suppress intracellular ice formation. Other CPAs, including hydroxyethyl starch (HES) and disaccharides like trehalose, act extracellularly to promote vitrification, minimize osmotic shifts, and protect membrane integrity.

Nature has also offered valuable insight. Freeze-tolerant organisms such as Antarctic fish and overwintering insects produce antifreeze proteins (AFPs) and antifreeze glycoproteins (AFGPs) that lower the equilibrium freezing point below that of the melting point. In addition, these natural glycoproteins also inhibit ice recrystallization and help maintain small, stable ice crystals during freezing and thawing.

Despite these advances, conventional CPAs are not without limitations. Although AFPs offer a compelling biological model, their strong ice-binding activity can induce dynamic ice shaping (DIS), resulting in sharp, elongated, spicular ice crystals that intensify cryoinjury. Their large and structurally complex nature also makes their cost-effective manufacturing challenging. In contrast, the relatively cheap CPA, DMSO, remains the gold standard, although it is cytotoxic and has been shown to dramatically impair post-thaw function. When administered to patients, DMSO can be associated with adverse side effects, underscoring the need for safer, more targeted preservation strategies.

IRIs come on the scene

To overcome these limitations, researchers have explored the development of synthetic ice recrystallization inhibitors (IRIs). These small molecules are specifically designed to mitigate the cellular damage from uncontrolled ice growth during cryopreservation and, ultimately, enable more flexible storage conditions and improve post-thaw cell recovery and viability, providing increased post-thaw quality. By reducing variability in post-thaw recovery and enhancing functional outcomes, this technology is redefining cryopreservation across a broad spectrum of applications. Pioneering

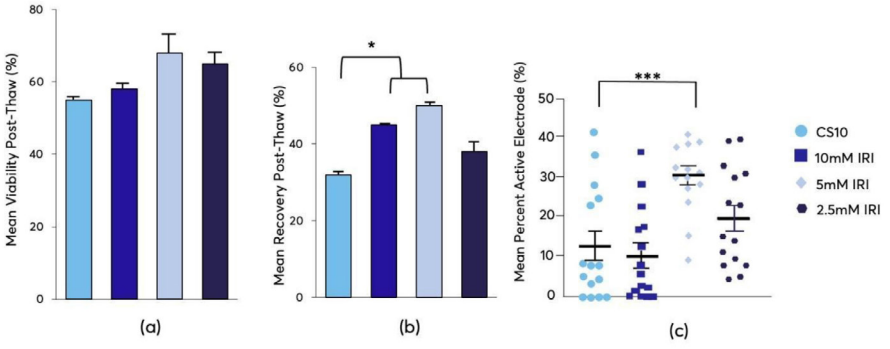


Figure 1: Cryopreservation and functionality of iPSC-derived forebrain neurons (iPSC-Ns). a) Percentage of post-thaw viability b) recovery (mean + SEM) c) mean percentage (mean ± SEM) of active electrodes at 236 days *in vitro* (DIV) of iPSC-N in CS10 and CS10 supplemented at different concentrations of IRI (2.5, 5, and 10 mM). Statistical significance marked by asterisks assessed by one-way analysis of variance (ANOVA) for comparison to control (CS10), where ns=p>0.05, *= p≤0.05 and, ***= p≤0.001 (n=3).[1,2]

work out of the University of Ottawa, Department of Chemistry and Biomolecular Sciences, demonstrated that small molecules could be rationally designed to mimic the IRI activity of natural AFPs without inducing dynamic ice shaping. Through iterative structure-activity studies, chemical scaffolds that potently inhibit ice recrystallization while remaining non-toxic, synthetically accessible, and highly tunable were identified. These compounds interfere with ice crystal growth kinetics, avoiding the sharp morphologies associated with AFPs.

PanTHERA CryoSolutions has advanced this work by developing proprietary IRIs that are compatible with conventional cryopreservation protocols. These compounds can be used in combination with traditional CPAs, providing a complementary mechanism of action that directly targets recrystallization—an under-addressed but significant source of cryoinjury, especially during transient warming or thawing. In doing so, they also enable the potential reduction of CPA concentration, helping to minimize cytotoxicity without compromising protection. By mitigating ice-induced mechanical damage and reducing variability in post-thaw cell recovery, IRIs represent a promising tool for improving the safety, reproducibility, and scalability of cryopreservation across multiple cell types and applications.

Results from IRI application

Cryopreservation outcomes vary widely depending on the cell type and stress conditions encountered, and IRIs can support them in different ways. As shown in *Figure 1*, the addition of IRIs to induced pluripotent stem cells (iPSCs) during cryopreservation can increase post-thaw viability and recovery without affecting pluripotency.[1,2]

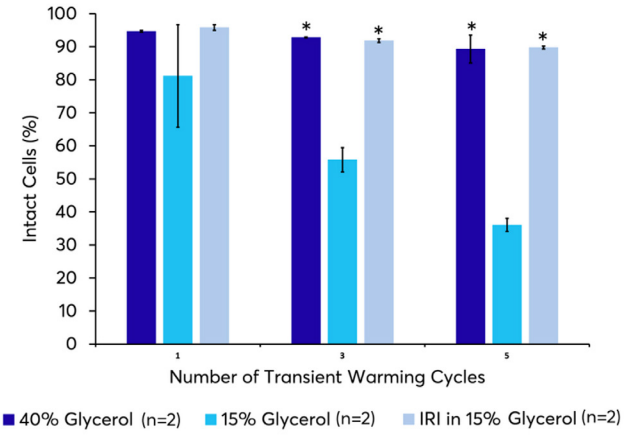


Figure 2: Red Blood Cells (RBCs) subjected to five transient warming events with and without IRIs were frozen by placement of vials in dry ice (-80 °C), partially thawed to -20 °C, and allowed to stabilize at -20 °C. The samples were then refrozen to -80 °C by again placing the vials in dry ice. This represents one cycle of transient warming (-80 °C to -20 °C to -80 °C). After one, three, and five cycles of transient warming, the samples were thawed in a +37 °C water bath and percent of intact RBCs was measured. Statistical significance marked by asterisks assessed by student's t-test for comparison to control (15% glycerol), where * = $p<0.05$.[2,4]

The inclusion of IRIs can also facilitate a faster reestablishment of neuronal network activity and synaptic function compared to controls for iPSC-derived neurons (iPSC-Ns) (*Figure 1*).[1,2]

A growing number of systematic studies and recent reviews now document these advantages of IRIs across multiple systems.[3] Platelet cryopreservation has shown measurable preservation of key surface markers and morphology with IRI supplementation, and hematopoietic stem and progenitor cells (HSPCs) cryopreserved with IRI-containing formulations have demonstrated improved post-thaw function and potency, including superior engraftment with umbilical cord (UCB) transplant models.

Beyond enhancing viability and functional recovery, IRIs also provide resilience to unintentional transient warming events (TWEs) during storage or handling—conditions that frequently lead to recrystallization-related injury and are difficult to control with conventional CPAs alone. For RBCs, the inclusion of IRIs during cryopreservation can not only enable the reduction of glycerol concentration while significantly improving membrane integrity, but as highlighted in *Figure 2*, RBCs with IRI can maintain higher integrity after repeated warming cycles.[2,4] The protective effects extend to complex tissue. Rat lungs and livers perfused with IRIs exhibited greater post-thaw membrane integrity compared to organs preserved with DMSO alone.[3]

Together, these data underscore the potential for IRIs to improve the consistency, safety, and scalability of cryopreservation across a wide range of clinically and commercially relevant cell types, including T cells, NK cells, CAR T cells, iPSCs, and more.

Why it matters

As cryopreservation becomes increasingly central to medicine, biotechnology, and conservation, the limitations of conventional cryoprotectants are becoming more apparent. Ice recrystallization is being increasingly recognized as a critical source of cryoinjury that compromises post-thaw cell quality and function. IRIs offer a targeted, next-generation solution to this challenge. By mitigating ice-induced damage, enhancing post-thaw recovery, and enabling reductions in cytotoxic agents like DMSO, IRIs improve both the safety and reliability of cryopreservation protocols. Their versatility across a wide range of cell types positions them as a foundational tool in the future of precision biopreservation. GEN

Rebecca Mercier, PhD, is a cell biologist at PanTHERA CryoSolutions, now part of BioLife Solutions. Ana Clementin, PhD, is the executive director at PanTHERA CryoSolutions, now part of BioLife Solutions. Jason Acker, PhD, is a professor at the University of Alberta, Department of Laboratory Medicine and Pathology, and co-founder of PanTHERA CryoSolutions, now part of BioLife Solutions. Robert Ben, PhD, is a professor at the University of Ottawa, Department of Chemistry and Biomolecular Sciences and co-founder of PanTHERA CryoSolutions, now part of BioLife Solutions.

References available online.

Giovanna Prout

COUNTABLE LABS

In her new role as CEO, Prout will focus on commercialization of products, drawing on leadership experience from Illumina, 10x Genomics, and Scale Biosciences to expand PCR applications across academic, translational, and clinical markets.

Neeraj Garg

ARAGEN

As CEO, Discovery Solutions, Garg will lead strategy, drive growth, expand client partnerships, boost operational efficiency, and foster innovation to accelerate partners' research programs—drawing on decades of leadership across life sciences and healthcare.

ITALFARMACO has welcomed **Francesco Di Marco, PhD**, as chief executive officer.

HUTCHMED has announced **Tan Shao Weng Daniel, MBBS, PhD**, as independent non-executive director and technical committee member.

VTV THERAPEUTICS has appointed **Alfonso Galderisi, MD, PhD, Mark Evans, MD, Chantal Mathieu, MD, PhD,** and **Klara Klein, MD, PhD**, to its scientific advisory board.

VALITOR has named **Gregory D. Kunst** as chief executive officer.

IMMATICS has confirmed **Venkat Ramanan, PhD**, as chief financial officer.

Keith Gottesdiener, MD, has joined **SEPTERNA's** board of directors.

ZYMEWORKS has designated **Adam Schayowitz, PhD**, as acting chief development officer.

RELMADA THERAPEUTICS has elected **Max Kates, MD**, to the clinical advisory board.

Brian Posner was appointed to **DYNE THERAPEUTICS'** board of directors.

Mark Hyman, MD, was designated as scientific and medical advisor of **ADVANTAGE THERAPEUTICS**.

FAIRJOURNEY BIOLOGICS has confirmed **Werner Lanthaler, PhD**, as chief executive officer.

Philippe Monteyne, MD, PhD, has joined as chairman of **BIOXODES'** board of directors.

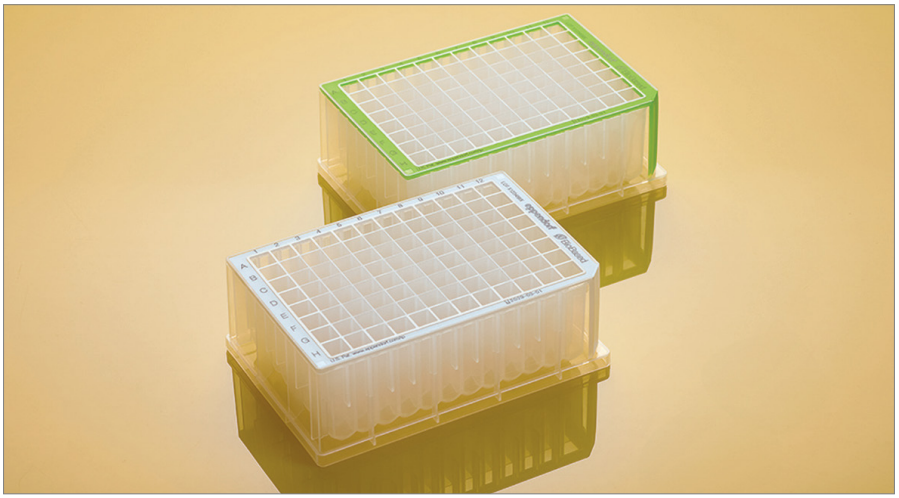
QUALIGEN THERAPEUTICS has elected **Jerry (Jiawei) Wang** as co-chief executive officer and Koti Meka as chief financial officer.

COMPANY INDEX

ADVERTISER INDEX

Products To Watch

BioBased Deepwell Plates



Eppendorf has introduced Deepwell Plates BioBased, made from approximately 95% second-generation feedstock. The plates are designed to reduce reliance on fossil-based plates while maintaining the same chemical resistance, thermal stability, and centrifugation performance as standard Deepwell plates. Available in a 96-well, 2 mL per well format, they are suitable for high-throughput screening, sample storage, and proteomics applications.

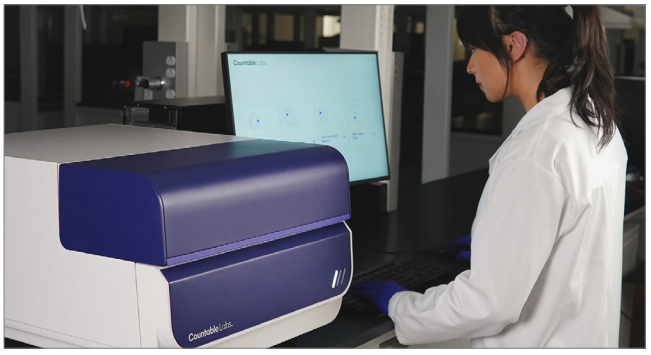
Eppendorf
www.eppendorf.com

AAV Total Capsid Quantification Kits

Abselion has introduced the AAVX Total Capsid Quantification Kit and the AAV9 Total Capsid Quantification Kit for use with its Amperia™ benchtop quantification platform. Both kits incorporate Thermo Fisher Scientific's CaptureSelect™ affinity reagents to provide high specificity and consistent performance across a range of adeno-associated virus (AAV) serotypes. The ready-to-use kits include sensor strips, assay plates, detection reagents, and buffers in a sandwich-style immunoassay format, enabling automated electrochemical detection of total AAV capsids from purified or complex samples.

Abselion
www.abselion.com

Ten-Color PCR Instrument



Countable Labs has launched Countable 10, a PCR instrument capable of detecting 10 distinct fluorophores within a single reaction. The system extends the company's Countable PCR technology, which performs single-molecule quantitation across millions of compartments. By expanding detection from four to ten colors, Countable 10 enables higher-throughput analysis and reduces spectral overlap, offering an alternative to next-generation sequencing for multiplex studies.

Countable Labs
www.countablelabs.com

XPS Depth Profiling Surface Analysis System

Thermo Fisher Scientific has introduced the Thermo Scientific™ Hypulse™ Surface Analysis System, designed to advance X-ray photoelectron spectroscopy (XPS) depth profiling for materials research. The system integrates femtosecond laser technology with the company's MAGCIS™ ion source to maintain sample integrity and facilitate characterization of materials at greater depths. It is intended to support applications across sectors such as energy storage and medical implants by providing improved insight into surface composition.

Thermo Fisher Scientific
www.thermofisher.com

All-in-One Organ-on-a-Chip System

CN Bio has launched PhysioMimix® Core, an integrated Organ-on-a-chip (OOC) platform that supports single-organ, multi-organ, and higher-throughput configurations within one system. The instrument is compatible with existing PhysioMimix accessories, consumables, and validated protocols, providing a workflow for modeling human physiology *in vitro*. Its tubeless microfluidic design minimizes contamination risk and maintenance requirements, while adjustable flow rates enable long-term and repeat-dosing studies across drug discovery and disease modeling applications.

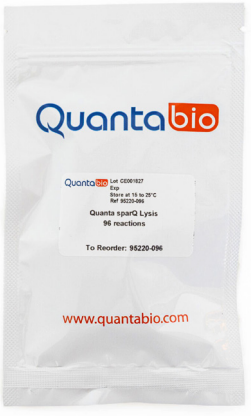
CN Bio
cn-bio.com

Cell-Free DNA Templates for mRNA Synthesis

Elegen has launched ENFINIA™ IVT Ready DNA, a cell-free gene synthesis platform that provides full-length linear DNA templates encoded poly(A) tails for *in vitro* transcription. The templates are delivered in as few as 10 business days and are free of bioburden, endotoxins, and recombination-mediated variation. The system aims to reduce processing steps and variability in the development of mRNA-based therapeutics.

Elegen
www.elegenbio.com

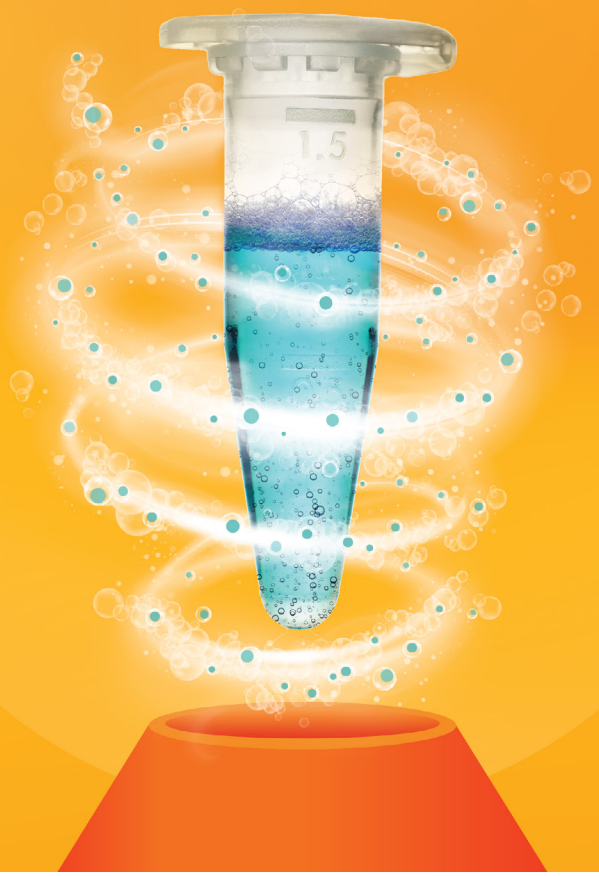
DNA Extraction Kit for Dried Blood Spot Samples



Quantabio has launched the sparQ™ Lysis Kit, designed to isolate high-quality, double-stranded genomic DNA from dried blood spot (DBS) samples. The kit enables DNA recovery from limited sample inputs and integrates with automated, high-throughput workflows. It supports applications such as whole-genome sequencing, qPCR, and digital PCR, providing a scalable solution for newborn screening and other genetic testing workflows.

Quantabio
www.quantabio.com

Revolutionizing single-cell sequencing with the new Illumina end-to-end solution



5×

more cells[1], more discoveries

7×

lower equipment costs[2]

No service contract

Only basic lab tools required

illumina®

To learn more,
download new ebook.

To reach out to our experts:
Phone: +1 800 809-4566 ext 1 (Toll Free)
Email: insidesales@illumina.com

1. Value: For the same price, you can process 5X more cells using Illumina Single Cell Prep than leading single-cell alternative
2. Equipment costs are 7X higher with leading single-cell alternative than Illumina Single Cell Prep