GEN Genetic Engineering & Biotechnology News

MARCH 2026

In Vivo CAR T Therapy

Will the Bets Pay Off?

A-List Top 10 Takeover Targets

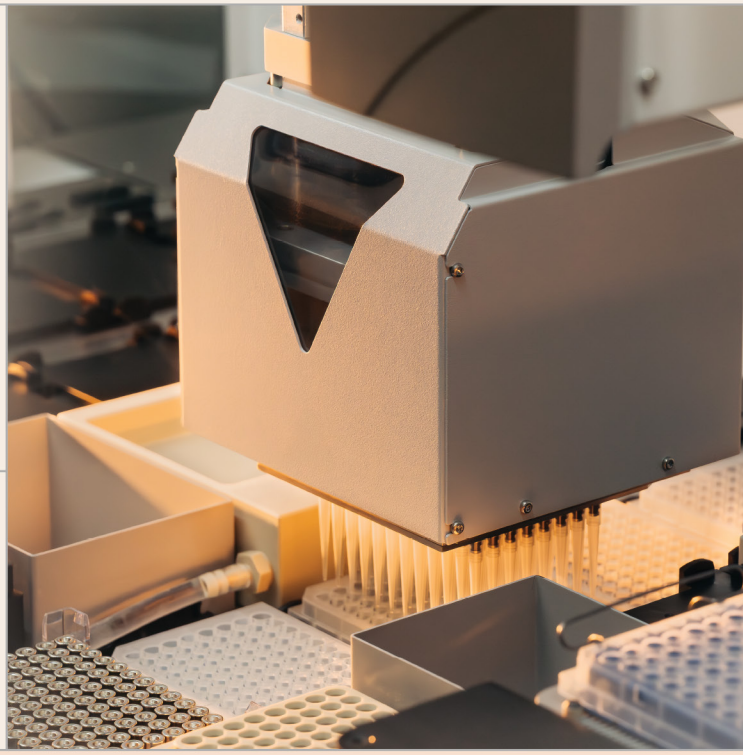
AI Unites
Regulation and Manufacturing

PPIs
Targeting the Undruggable

AgBio's Future
Where Crops meet CRISPR

Establish a new standard in proteomics

Illumina Protein Prep combines an innovative aptamer-based proteomics assay with NGS readout and integrated data analysis, delivering a high-throughput, highly scalable solution to maximize proteomics discovery power.



9.5K
Human protein targets

200+
Biological pathways

1
Panel

Fastest, streamlined workflow

2.5 days
from sample to answer

4 hr
hands-on time

1 platform
for proteomics assay and library preparation automation

Step 1: Automation
Proteomics assay

Step 2:Automation *
Library preparation

Step 3
Sequencing

Step 1
Analysis

*Proteomics assay and library preparation are both automated on the Illumina Protein Prep Automation System, a custom Tecan Fluent 780.

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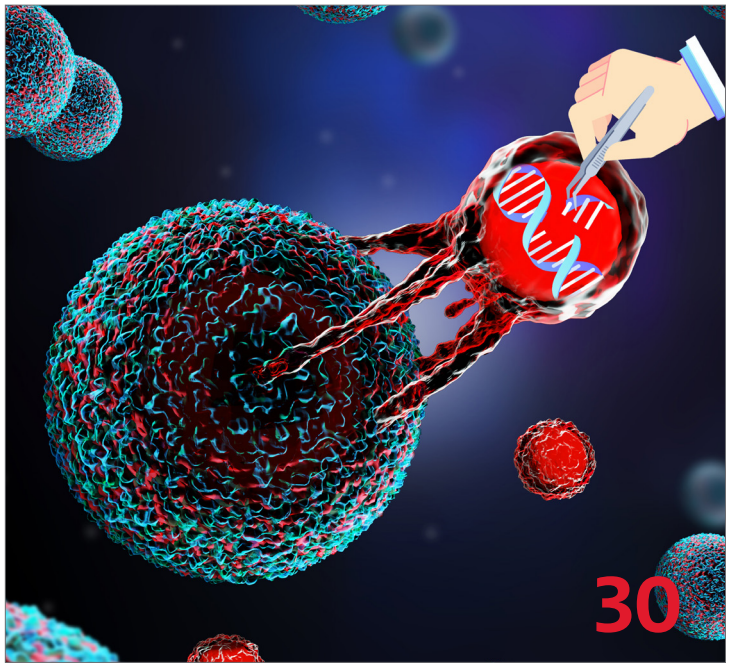


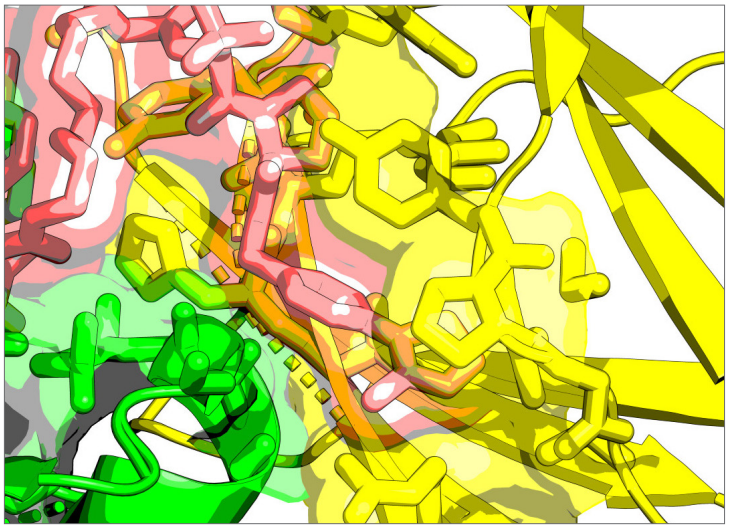
In Vivo CAR T Therapy

Will the Bets Pay Off?

With clinical data beginning to emerge, big pharma is signaling its belief that *in vivo* CAR generation is the next immunotherapy breakthrough.

A-LIST

DRUG DISCOVERY



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

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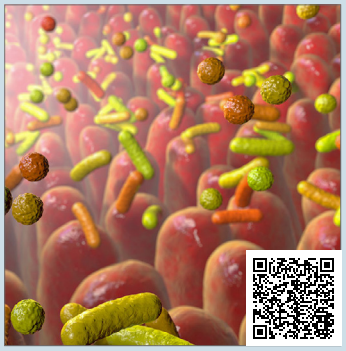
Opentrons Uses Nvidia Tech to Build Training Data That Powers Physical AI in the Lab



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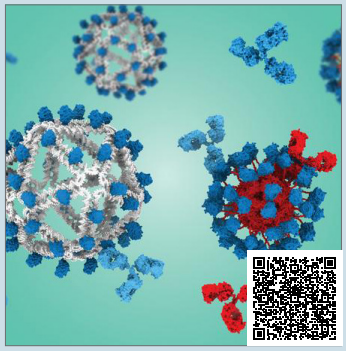
Previously Unknown Gut Bacteria Emerge as Global Marker of Health

Iambic Therapeutics

Takeda, Iambic Launch Up-to-$1.7B AI Collaboration



MIT and Scripps Research

New HIV Vaccine Scaffold Primes Rare B Cells for Broadly Neutralizing Responses

Cover Image: Meletios Verras / iStock / Getty Images Plus *and* Tetiana Lazunova / iStock / Getty Images Plus

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BIOPROCESSING

DEPARTMENTS

FUJIFILM
FUJIFILM Biosciences

FUJIFILM Irvine Scientific is Now FUJIFILM Biosciences

A full-spectrum provider of life sciences solutions built from a 55-year history as a cell culture pioneer

The FUJIFILM Biosciences name builds upon our roots as a pioneer in the cell culture media industry. Now, through a core focus on people, innovation, and quality, we serve a much broader life science community.

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From the Editor in Chief

"We don't have love at first sight on Mars. Either it was too silly to bother with, or it was something we discarded in our Dusk Ages."

—Uncle Martin (The Martian)
from the 1960s TV sitcom, *My Favorite Martian*

John Sterling

The global space economy reached a record $613 billion in 2024. Most of the money is largely driven by the idea, more than a few would say the *need*, to travel to other planets. This is nothing new to the world's imagination. "Back in the golden age of science fiction, most stories involved space exploration," writes Kirk McElhearn in August 2024 in the *L&L Blog*.

A Pew Research Center survey in July 2023 found that 55% of Americans foresee regular space tourism during the next five decades. Well, Scott Solomon, PhD, teaching professor of bioscience at Rice University, goes a major step further in his new book, *Becoming Martian: How Living in Space Will Change Our Bodies and Minds*.

Solomon not only discusses traveling to Mars but settling it. During this process, humans will become much more than colonizers. Humanity will be transformed. Maybe even into a new species.

Mars is hostile to humans. Thin atmosphere, low gravity (38% of Earth's), strong radiation exposure, extreme cold, and toxic soil. If humans ultimately settled Mars, natural selection, genetic drift, and possibly genetic engineering would shape Martians of the future. Adaptations might include denser bones or altered skeletal structure due to the low gravity, changes in immune systems, increased radiation resistance, and, interestingly, reproductive changes.

Thus, colonizing Mars is more than an engineering challenge. It's also a biological one. Studies of island life such as in the Galápagos have shown that gene flow between isolated populations represents a key factor in determining if an island population evolves into a new species.

"The take-home message from all our island exploration is this: The more movement of people back and forth between Earth and Mars, the less likely it will be for people on Mars to evolve into a new species. That is, as long as people from both planets exchange genes by having children together, a new species of human is less likely to evolve on Mars," writes Solomon, who adds an additional thought.

"To undergo speciation and truly become Martians, something would need to limit reproduction between Earthlings and Martians. That something might come from the things we bring with us, whether we realize it or not."

I've been thinking about how to overcome that potential "something." Maybe experiencing love at first sight?

John.Sterling@sagepub.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.

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Mary Ann Liebert
A Part of Sage

Sticky ends

Breathing in the Past

A study in *Frontiers in Environmental Archaeology* introduced a new framework for translating biomolecular data from archaeological materials into scent recreations. Recent work revealed that ancient objects can retain the molecular fingerprints of past aromatic practices. These molecules provide unprecedented insight into ancient perfumery, medicine, ritual, and daily life.

Researchers developed two formats for presenting ancient scents in public settings. They created a portable scented card and a fixed scent diffusion station integrated into exhibition design at the Moesgaard Museum in Aarhus, Denmark. "The Scent of the Afterlife" card recreates some of the aromas that accompanied the ancient Egyptian mummification process.

Museum August Kestner, Hannover, Germany; Ehrich, SC, et al

Visitors sniffing the "Scent of the Afterlife" card during a guided tour at the Museum August Kestner in Hanover, Germany, experience smell sensations inspired by the artifacts on display. The scented cards have quickly become an integral part of the tour.

Delius / iStock / Getty Images Plus

Ice Age Microbial Ally

Paun VI. — Scarisoara Ice Cave in Romania

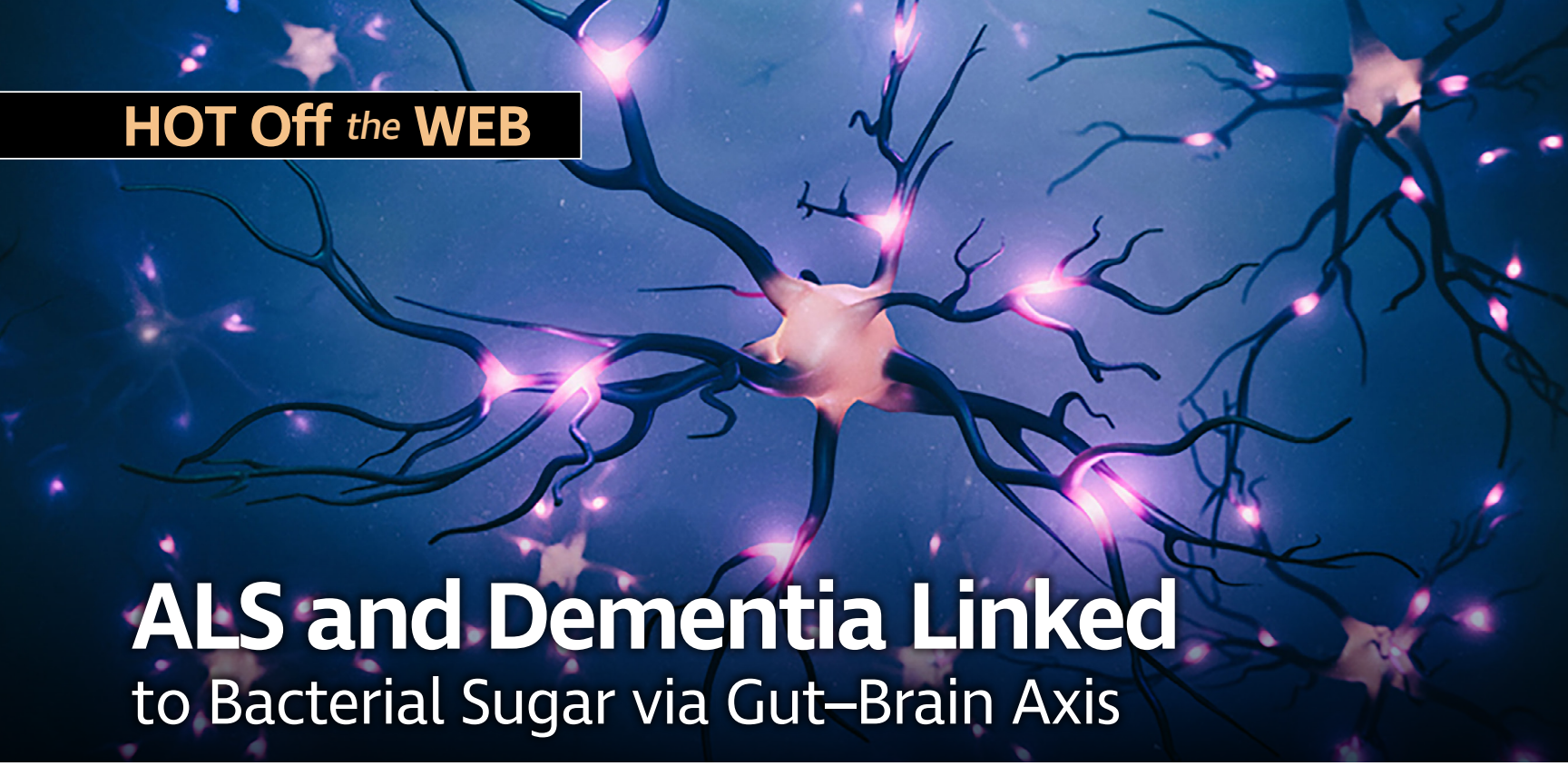
Ice caves host a variety of bacteria that represent a source of genetic diversity that has not yet been studied extensively. Now, researchers in Romania have published the first genome sequence and functional profiling of a *Psychrobacter* strain preserved in 5,000-year-old cave ice. The team analyzed its antibiotic resistance profile, opening new opportunities to develop strategies to combat the rise of resistance and better understand how it naturally evolves and spreads.

"The *Psychrobacter* SC65A.3 bacterial strain isolated from Scarisoara Ice Cave, despite its ancient origin, shows resistance to multiple modern antibiotics and carries over 100 resistance-related genes," said Cristina Purcarea, PhD, a senior scientist at the Institute of Biology Bucharest of the Romanian Academy. "But it can also inhibit the growth of several major antibiotic-resistant 'superbugs' and showed important enzymatic activities with important biotechnological potential."

Sense, Sensibility, and Whiskers

Like many other mammals such as cats and rats, elephants have whiskers. Indeed, there are thousands of nonmoving whiskers spread across the thick skin of the trunk. Now, new research reveals that the sensitivity of the elephant trunk is partly powered by whiskers whose material structure changes from base to tip.

The research team from Max Planck Institute for Intelligent Systems used micro–computed tomography imaging, electron microscopy, mechanical testing, and finite element analysis to characterize the geometry, porosity, and stiffness of whiskers from both young and adult Asian elephant whiskers. The findings show that the material properties of elephant whiskers transition from thick, porous, and stiff at the base of the trunk to thin, dense, and soft at the tip. This unique property amplifies sensory signals, allowing elephants to feel their surroundings through their trunks with remarkable precision.



ALS and Dementia Linked to Bacterial Sugar via Gut–Brain Axis

Neurons [Evgenii Kovalev / E+ / Getty Images]

In a new study published in *Cell Reports* titled, "*C9orf72* in myeloid cells prevents an inflammatory response to microbial glycogen," researchers from Case Western Reserve University have identified a link between gut bacteria and the deterioration of the brain in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). Results identified bacterial sugars that cause neurodegenerative immune responses, providing a mechanism for therapeutic intervention.

The human gastrointestinal tract is a large source of neuromodulatory factors and represents the largest site of microbial–host interactions, with an estimated 100 trillion microorganisms interfaced by 70%–80% of the body's immune cells. Disruption to the microbe-immune-brain axis may contribute to neurodegeneration risk. However, how the gut microbiome is altered in patients with ALS is not understood.

"We found that harmful gut bacteria produce inflammatory forms of glycogen, and that these bacterial sugars trigger immune responses that damage the brain," said Aaron Burberry, PhD, assistant professor in the department of pathology at the Case Western Reserve School of Medicine and co-corresponding author of the study.

FTD mainly affects the brain's frontal and temporal lobes, causing changes in a person's personality, behavior, and language. ALS primarily targets motor neurons, resulting in gradual muscle weakness and paralysis. While most causes of ALS and FTD cases are unknown, researchers have investigated the role of genetics, environmental issues, brain injuries and diet in neurodegeneration.

The authors reported that 70% of the 23 ALS/FTD patients examined had dangerous glycogen levels. Only one third of patients without the brain diseases displayed high levels of glycogen.

The study has immediate implications for patient care by identifying new targets to treat ALS and FTD, while providing biomarkers to identify patients who might benefit from gut-targeted therapies. New treatments can break down harmful sugars in the gut while opening the door to developing drugs that target the connection between the digestive system and the brain.

Alex Rodriguez-Palacios, DVM, PhD, assistant professor in the Digestive Health Research Institute at the School of Medicine and co-corresponding author of the study, said reducing the harmful sugars "improved brain health and extended lifespan."

The discovery is particularly significant for *C90RF72* mutation carriers, the most common genetic cause of ALS and FTD. The research explains why some people with the mutation develop the diseases while others do not, identifying gut bacteria as a key environmental trigger.

The study was possible due to Case Western Reserve's unique ability to conduct studies using germ-free mouse models, which allowed the researchers to study how specific gut bacteria affect brain diseases. While traditional methods could only accommodate a few mice at a time, the design allows large-scale microbiological studies for understanding the complex communication between the gut and brain.

Burberry says the team will next conduct larger studies surveying gut microbiome communities in ALS/FTD patients before and after disease onset to understand when and why harmful microbial glycogen is produced. He notes that clinical trials to determine whether glycogen degradation in ALS/FTD patients could slow disease progression are supported by the findings and could begin in a year. GEN

DeepMind's AlphaGenome Predicts
Genetic Variation Function, Including Disease

Small variations in DNA sequence can alter an organism's response to the environment or susceptibility to disease. Interpreting the impact of genome sequence variation remains a research challenge. Non-coding variants that lie outside of protein-coding regions are particularly difficult to interpret because of the diversity of molecular consequences.

The Google DeepMind team behind Nobel Prize winning AlphaFold has now published AlphaGenome, a DNA sequence model that advances regulatory variant-effect prediction to understand genome function, in *Nature*.

AlphaGenome's applications include the identification of new therapeutic targets and design of synthetic DNA with specific regulatory function. The authors state that AlphaGenome is particularly suitable for studying rare variants with potentially large effects, such as those causing rare Mendelian disorders.

"Determining the relevance of different non-coding variants can be extremely challenging, particularly to do at scale," said Marc Mansour, PhD, a professor at University of College London who focuses on hematological malignancies. "This tool will provide a crucial piece of the puzzle, allowing us to make better connections to understand diseases like cancer."

AlphaGenome takes a long DNA sequence, up to one million base pairs, as input, and predicts thousands of molecular properties characterizing regulatory activity, including locations of where genes begin and end in different cell types and tissues, splicing sites, RNA production, and DNA accessibility.

This long sequence context is crucial to cover regions that are regulated by distant genes. Previous models had to trade off sequence length and resolution, which limited the range of modalities that could be modeled.

In efficiency, AlphaGenome is reported to score the impact of a genetic variant on a range of molecular properties in one second by comparing predictions of mutated and unmutated sequences.

Many rare genetic diseases, such as spinal muscular atrophy and some forms of cystic fibrosis, can be caused by errors in RNA splicing. Notably, AlphaGenome can explicitly model the location and expression level of these junctions directly from sequence, offering deeper insights about the consequences of genetic variants on RNA splicing.

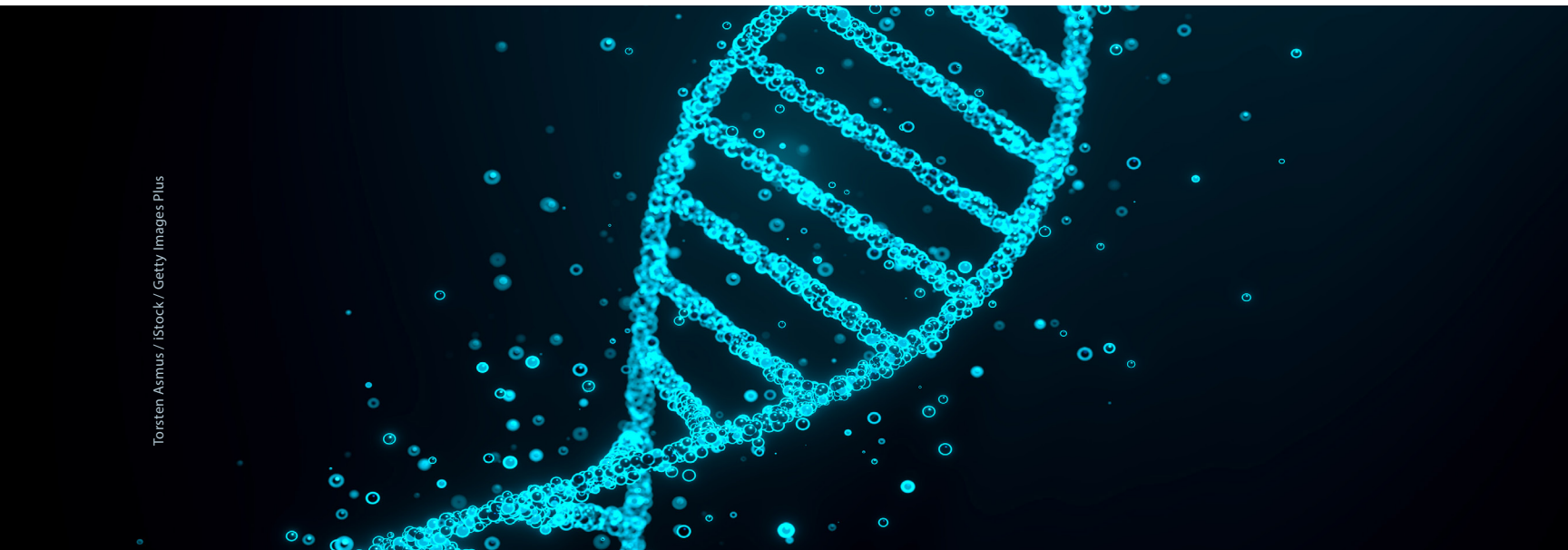
"For the first time, we have a single model that unifies long-range context, base-level precision and state-of-the-art performance across a whole spectrum of genomic tasks," said Caleb Lareau, PhD, principal investigator at Memorial Sloan Kettering Cancer Center.

Training data was sourced from large public consortia including ENCODE, GTEX, 4D Nucleome and FANTOM5, which experimentally measured gene regulation properties across hundreds of human and mouse cell types and tissues.

In future work, the authors note that accurately capturing the influence of regulatory elements at large distances, such as those that are 100,000 DNA letters away, remains a limitation for AlphaGenome. Another priority is to improve the model's ability to capture cell and tissue-specific patterns.

Additionally, AlphaGenome characterizes the performance on individual genetic variants and has not been validated for personal genome prediction. Additionally, while AlphaGenome predicts molecular outcomes, how genetic variations lead to complex traits or diseases involve broader biological processes, such as developmental and environmental factors, that are beyond the direct scope of the model.

DeepMind has made AlphaGenome available for non-commercial research. GEN



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Fully Continuous Bioprocessing
Drops mAb Costs

By Gail Dutton

Enzene's New Jersey facility offers efficient, fully continuous or hybrid vat production within a modular framework

Continuous biopharmaceutical manufacturing is expected to grow as much as 17% between now and 2033, according to multiple industry analysts, thanks to its ability to improve efficiency, enhance quality, and reduce costs when compared to batch processing. For manufacturers, implementation can be a fully continuous model, or a hybrid approach that gradually phases in continuous processing while leaving some processes distinctly separate.

Enzene, a global contract development and manufacturing organization (CDMO), is one of the first to offer fully connected continuous manufacturing (FCCM™) technology. FCCM's modular approach enables manufacturers to evolve their processes to a fully continuous model gradually, linking and automating sections at a time while still running other sections of the process traditionally.

Using this system, Himanshu Gadgil, PhD, CEO of Enzene, says, "In 2025, we hit our stated target to achieve monoclonal antibody (mAb) production costs of less than $40 per gram."

For context, other continuous processing methods average $80 to $100 per gram, while fed-batch processes may range from $150 to $300 per gram, according to Russell Miller, Enzene's vice president of global sales and marketing.

Commercial biologics validation

Enzene's recent claim to fame is its modular, FCCM-powered EnzeneX™ platform. With that platform, Enzene won the 2025 CPHI Pharma Award for Manufacturing Excellence last October. EnzeneX is considered to be the first truly fully connected continuous manufacturing technology to be validated for commercial biologics applications. So far, four mAbs have been commercialized using FCCM technology, including, most recently, pertuzumab.

Because FCCM technology is modular, it also can run as a semi-continuous hybrid system in which only certain elements operate continuously. An example would be to run protein capture continuously, but halt before running other downstream steps. Such modularity helps companies retrofit continuous components into their existing batch processes.

"The platform is fully connected from bioreactor to pre-drug substance, with everything happening simultaneously in continuous mode," Gadgil says. Yield is tenfold greater than conventional batch manufacturing, which supports savings—in terms of cost of goods sold—as high as 40 to 50%, "even for complex molecules."

"Traditionally," Miller elaborates, "biologics manufacturing requires multiple large bioreactors operating in sequence, often involving up to six massive tanks and consuming substantial space, capital, and time, and introducing operational risks. With FCCM technology, however, fresh media is continuously fed into cell cultures, linking reaction, separation, and purification into a single streamlined process."

"This approach maximizes reactor utilization and increases output by using optimized cell media and process analytical technology," he says. "This significantly reduces costs and minimizes risks." Furthermore, FCCM's modular technology supports ready scale-up.

Miller points to an FCCM footprint that he says is 70% smaller than that of comparable batch cultures. That, combined with the ability to use a smaller clean room, reduces the carbon footprint per gram of protein produced.

From India to New Jersey

Enzene was formed in 2015 in Pune, India, as a clone-to-formulation facility and clinical manufacturing facility. By about 2020, coincidental with the outbreak of the COVID-19 pandemic, its operations morphed to include CDMO operations.

Since then, much of its early-stage biologics work—especially around Phase I manufacturing—has been for U.S.-based companies. "Many potential clients expressed a preference for a local partner to avoid time-zone friction, supply chain complexity,

Vital SIGNS

Enzene

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Principal
Himanshu Gadgil, PhD, CEO

Number of Employees
700+

Focus
A continuously innovative development and manufacturing organization.

and post-COVID operations risks," Gadgil recalls. Therefore, the company began planning for U.S.-based operations.

Even without that stated preference, the U.S.—a leader in early-stage biologics innovation with a dense concentration of innovative companies—was an attractive market. Increasing interest in reshoring biomanufacturing to the U.S. accelerated the timeline, Gadgil admits, "but building a presence in the U.S. was already a long-term, client-led decision that aligned with where biologics development is happening fastest today."

Enzene opened its first U.S. facility in New Jersey in September 2025. The 80,000 square-foot manufacturing center features the EnzeneX platform and the FCCM technology.

"Now that it has established operations in the U.S., Enzene will turn to anchoring the business," Gadgil says. "We expect to significantly expand our U.S. manufacturing capacity over the next few years in support of a growing deal funnel across a broad range of biomodalities."

Small innovators and big pharma

Enzene works with clients of all sizes, the company is quick to underscore.

"Many large CDMOs operating with 10,000–20,000-liter capacities prefer working with big pharma," Miller acknowledges, "but early-stage companies often struggle to find the right partner, especially one that is local. That's where we provide solutions." Rapid onboarding for early-stage clients is a major differentiator, he points out. He stresses the flexibility that comes from modularity and the ability to right-size manufacturing "for clients from early-stage supply to commercialization."

Big pharma is becoming particularly interested. "We are in discussions with several top 10 pharma companies," Miller says. "So, while early-stage companies will stay an important segment, our platform's flexibility, scalability, footprint advantages, and efficiency appeal strongly to large pharma as well, and interest is growing rapidly."

Challenges equal opportunities

The health of the biotech industry is generally good, even though sales margins face increasing pressure. In such an environment, Miller suggests, there are opportunities for companies of all sizes to leverage the EnzeneX platform to enhance biomanufacturing efficiency and thereby lower costs.

He also says that flexible manufacturing platforms can help overcome challenges in a still-fractured global regulatory environment. Specifically, Miller emphasizes the ease of advancing programs from lab to commercial scale while maintaining batch consistency and adherence to good manufacturing practice standards.

Enzene also has developed another revenue stream, manufacturing therapeutics for both human and animal health markets. "Animal health is a logical adjacency to our core capabilities," Miller emphasizes.

In terms of maturity, the animal health market is at the point human biotherapeutics were at ten years ago, Miller says. "Now there's huge potential for that segment to make giant leaps in supply models through the use of modern bioprocessing technologies."

The science-first concepts Enzene espouses, coupled with deep biologics expertise, regulatory discipline, and manufacturing platforms designed expressly for flexibility, scalability, productivity, and cost efficiency, "apply just as well to the animal health market as to the human health market," Miller reiterates. He suggests the current gap between market demand and manufacturing infrastructure for animal health products offers an opportunity.

Continual improvement

Having just completed an international expansion, it would be unremarkable for a company to pause to grow into its new market. With Enzene, this is not the case.

"We are not content to stand still," Gadgil says. "We are well-advanced in our efforts to bring a new generation of the EnzeneX platform to market. The key point for us is that achieving these cost and efficiency improvements is not a one-off outcome; it's a repeatable, scalable cost structure built into the platform. GEN

From its Pune, India headquarters, Enzene developed the EnzeneX™ platform that not only provides fully continuous bioprocessing, but also enables modular integration that automates only customer-specified processes.

A-List

Top 10 Takeover Targets of 2026

Jacob Wackerhausen / iStock / Getty Images Plus

Despite Merck's comfort with M&A in the "tens of billions" of dollars, the year's first deals reflect caution among buyers

By Alex Philippidis

The year has gotten off to a warm start, though not quite red hot, when it comes to biopharma merger-and-acquisition (M&A) deals.

Market watchers rang in 2026 expecting the value and number of biopharma M&A deals to accelerate. Indeed, **Merck & Co.'s** chair and CEO, Rob Davis, JD, generated buzz at the recent J.P. Morgan 44th Annual Healthcare Conference when he spoke freely about the pharma giant's interest in big-dollar M&A. When J.P. Morgan Chase analyst Christopher Schott asked Davis what size deals would make Merck comfortable, the chief executive replied: "I would say we're multi-tens of billions of dollars."

But as of this article's deadline on February 13, the deals have been below that 10-figure range, which is associated with "blockbuster" M&A. **Eli Lilly** alone accounted for two buyouts in the first six weeks of this year, agreeing to buy **Ventyx Biosciences** for $1.2 billion and **Orna Therapeutics** for up to $2.4 billion. **GlaxoSmithKline** (**GSK**) in January committed $2.2 billion to acquire **Rapt Therapeutics,** the inflammatory and immunologic disease drug developer, while **Amgen** shelled out up to $840 million to buy privately held **Dark Blue Therapeutics**, a U.K.-based developer of small molecule-targeted protein degraders to treat cancer.

As for Merck, it reportedly walked away from a roughly $30 billion buyout of **Revolution Medicines** after the companies failed to come to terms on a price, though neither company has confirmed that.

However, Revolution has generated enough speculation among analysts, investors, and other market watchers that it is among the 10 companies highlighted in this year's edition of *GEN's* annual A-List of 10 biopharma companies seen as buyout targets in recent months. This A-List is based on notes to investors and comments in news outlets. For each company mentioned, the list explains where talk of acquisition has surfaced, and why, as well as where their primary stocks are traded.

Since first published in 2013, *GEN's* annual A-Lists of top takeover targets have pinpointed some companies just before they were acquired. The 2025 A-List included **Blueprint Medicines**, which found a buyer when **Sanofi** spent up to $9.5 billion to buy the company in a deal completed last July. The 2024 A-List also featured one company that has since been bought out by a biopharma giant: **Intra-Cellular Therapies** (by **Johnson & Johnson** last year for $14.6 billion).

The J&J-ICT deal was the largest of 2025, a year that saw the dollar value of biopharma M&A deals jump year-over-year from $90 billion to $149 billion, even as the number of deals fell from 90 to 76, according to EY-Parthenon.

This year marks the first takeover targets A-List *GEN* has ever published that does not include **BioMarin Pharmaceutical** among the top 10. The rare genetic disease drug developer appears to have shifted its approach to M&A under Alexander Hardy, who became president and CEO in December 2023, to one of buying companies rather than looking to be bought. Last year, BioMarin spent approximately $270 million to acquire **Inozyme** in a deal completed last July, followed in December by its agreement to purchase **Amicus Therapeutics** for $4.8 billion, a transaction expected to close in the second quarter. ■

Abivax
(Euronext Paris: ABVX)[1]

The Paris-based developer of oral, small-molecule drugs targeting microRNA-124 to treat chronic inflammatory diseases has become the most talked-about biotech takeover target since the summer, when it reported dazzling Phase III data surpassing company expectations for lead pipeline candidate obefazimod, an oral ulcerative colitis treatment. Abivax's stock surged an eye-popping 1,700% last year: "There is no doubt this drug is special. It's going to be a blockbuster," CEO Marc de Garidel told *GEN* in July 2025. Wall Street largely agrees: "We view ABVX as a compelling play in a commercially de-risked market, a potential take-out darling with strategic appeal, and upside to broader I&I [immunology and inflammation] indication optionality beyond ulcerative colitis/Crohn's disease," Gregory Renza, MD (Truist Securities) wrote in November. A month later, a survey by the firm showed 44% of investors citing Abivax as a buyout candidate. In January, French news outlet *La Lettre* reported that Eli Lilly was pursuing a potential €15 billion ($17.4 billion) Abivax acquisition—but France's finance ministry denied to Reuters having any contact with Lilly, which declined comment.

Celcuity
(NASDAQ: CELC)

The cancer drug developer drew close attention in November from Kalpit Patel (Wolfe Research). In addition to initiating coverage of Celcuity's stock with an Outperform rating and $110 price target, Patel concluded that Celcuity represented "a top-tier acquisition opportunity for big pharma" that was "primed to deliver next year" on key clinical data. Celcuity expects a Q1 or Q2 data readout from the cohort of its Phase III VIKTORIA-1 trial (NCT05501886) assessing lead candidate gedatolisib plus fulvestrant with and without palbociclib in adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *PIK3CA* mutant tumors, locally advanced or metastatic breast cancer, following progression on or after treatment with a CDK4/6 inhibitor and an aromatase inhibitor. In December, Celcuity presented positive data for the trial's *PIK3CA* wild-type cohort, showing median progression-free survival (PFS) of 12.4 months for gedatolisib-palbociclib-fulvestrant, 10.0 months for gedatolisib-fulvestrant, and just 1.9 months for fulvestrant alone.

Inventiva
(Euronext Paris: IVA)[2]

Shares of **Daix**, France-based **Inventiva**, surged more than 75% in the six months ending February 12 on speculation that later this year, the oral small-molecule developer focused on fibrosis, lysosomal storage disorders and oncology will release Phase III data for its lead candidate lanifibranor in metabolic dysfunction-associated steatohepatitis (MASH) that will show potentially the best efficacy to date. "Flag IVA as binary play with high takeout potential on Phase III data 2H26E," Lucy Codrington (Jefferies) wrote on February 2. Five months earlier, in September, Ananda Ghosh, PhD, (H.C. Wainwright) pegged Inventiva as a takeover target, declaring that lanifibranor "stands out" as the only pan-peroxisome proliferator-activated receptor (PPAR) agonist in Phase III that had already shown dual histologic benefit in Phase IIb studies, where it reduced both liver fibrosis and inflammation while simultaneously improving metabolic health, such as insulin sensitivity and lipid profiles.

MapLight Pharmaceuticals
(NASDAQ: MPLT)

The drug developer focused on neurological and neuropsychiatric disorders has built what Andrew Tsai (Jefferies) calls an intriguing pipeline led by the oral M1/M4 agonist ML-007C-MA, set to read out Phase II data in schizophrenia and Alzheimer's disease (AD) psychosis this year and in 2027. "ML-007's program success could attract big pharma attention," Tsai wrote in November. The following month, he said MapLight was among potential beneficiaries of a recent **Bristol Myers Squibb** (**BMS**) clinical setback: BMS delayed to year-end 2026 its data readout from the Phase III ADEPT-2 trial (NCT06126224) assessing Cobenfy™ (xanomeline and trospium chloride) in AD psychosis, opting to add more patients to the study after citing "irregularities" linked to the execution of the trial "at a small number of study sites." In October, MapLight completed a successful initial public offering (IPO), raising $269.8 million in net proceeds from selling 17,439,207 shares at $17 per share.

Qiagen
(NYSE: QGEN; Frankfurt Stock Exchange: QIA)[3]

The provider of biotech workflow solutions (officially based in Venlo, The Netherlands with operative HQ in Hilden, Germany) saw its stock price return to the $50 per-share range following three years of mostly lumbering between the high $30s and mid $40s, after *Bloomberg News* reported that Qiagen was evaluating strategic options that include a potential sale—a report attributed to unnamed sources—amid fresh interest from would-be buyers in acquiring the company. While Qiagen has declined to comment, "This potential sale does not come as a surprise to investors, as the company has long been viewed as a takeout candidate," wrote Casey Woodring (J.P. Morgan). Indeed, **Thermo Fisher** offered to acquire Qiagen in 2020, but the offer was terminated five months later. **Bio-Rad Laboratories** reportedly pursued a buyout deal in 2022. "We see potential strategic interest from several scaled tools companies given prior passes from TMO and BIO," Tycho Peterson (Jefferies) wrote in January, without naming them: "Now more than ever, a deal makes sense, in our view."

Revolution Medicines
(NASDAQ: RVMD)

The developer of RAS-addicted cancer therapies appears to have attracted several would-be suitors in recent months. **AbbVie** flatly denied being one of them, while Merck & Co. never commented on news reports, it tried to buy Revolution but gave up. "The two couldn't come to an agreement on price," according to unnamed sources cited by *The Wall Street Journal*, which reported that the companies discussed a deal in the $30 billion range. Behind buyers' interest is Revolution's clinical and preclinical pipeline of RAS(ON) inhibitors led by daraxonrasib, which is in four Phase III trials—three in forms of pancreatic ductal adenocarcinoma (PDAC) and one in locally advanced or metastatic RAS mutant non-small cell lung cancer (NSCLC). Daraxonrasib is poised to become the new standard of care in RAS-mutated advanced pancreatic cancer, Sean McCutcheon, PhD, (Raymond James) wrote in September.

Structure Therapeutics
(NASDAQ: GPCR)

The developer of oral small-molecule drugs for chronic metabolic and pulmonary diseases draws investor interest from being in the popular obesity segment. Structure's lead candidate aleniglipron, a selective GLP-1 receptor agonist, is set to advance to a Phase III trial in mid-2026 after reporting positive data in December from the Phase IIb ACCESS (NCT06693843) and ACCESS II (NCT06703021) trials showing placebo-adjusted weight loss after 36 weeks of 11.3% (27.3 lbs) with the 120 mg dose and up to 15.3% (35.5 lbs) with the 240 mg dose. Structure's shares more than doubled on the news—with Andy T. Hsieh, PhD, (William Blair) reporting that the surge was "likely driven by the M&A prospect" and "large market opportunity," plus speculation about aleniglipron gaining FDA approval after **Novo Nordisk's** oral Wegovy® (semaglutide), approved in December, and Eli Lilly's orfoglipron, under review with an April 10 target decision date.

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A Noble Pursuit: A Long-Time **AI-in-Biotech Skeptic** Takes Another Look

By Tim Harris, PhD

Yielding at the intersection of AI and biotechnology

Tim Harris, PhD
Operating Partner
SV Health Investors

Tim Harris, PhD, is a British biotech veteran entrepreneur and author of "In Pursuit of Unicorns" (*Cold Spring Harbor Lab Press, 2024*).

It is time we talked about artificial intelligence (AI). I have always been a bit of a skeptic about how important AI will be for the biotechnology industry, but, given a few of the companies that have formed and the amount of money they have raised, it seems I should take another look, and perhaps may even change my mind. The generation of scientists who trained in the late eighties and nineties and onwards are very much more computer savvy than I am. I am barely (by their standards) computer-literate. I was asked the other day what ChatGPT was, and I had to go to Google to look it up. Don't forget I am from the NEANMP ("no email and no mobile phones") era, and had P&Q (peace and quiet) when there was no intrusive social media to contend with.

But I can observe from my usual perch halfway up the tree. I see that there are different types of AI companies being set up. Those that are mostly focused on AI technology and moving the state of the art forward in molecular dynamics and writing programs to identify better ways to predict protein–protein and protein–small molecule interactions. There are also companies that use these applications to design better antibodies or suggest what small molecules might be synthesized to agonize or antagonize particular enzyme–substrate partners or ligand-receptor interactions. They then make the molecules and test them with a view to obtaining better drugs that affect those interactions more quickly. The companies developing the software and the novel algorithms for selecting high-quality "binders" face competition from public domain open-source programs (e.g., Boltz-2 and others) that can do many of the things that the companies are also doing. Considerable amounts of money have been raised by these companies (e.g., Chai Discovery) and also by AI franchises that intend to become drug makers, such as Isomorphic Labs and Xaira Therapeutics.

Whatever type of AI company—if you are in the drug discovery business—the fun starts at the point where you have done things called "experiments" to test the output of your AI-designed drugs in both *in vitro* and *in vivo* assays to find out if you are right in the real world. Sometimes these assays need to be developed first, which of course adds additional time to the process. AI can play a role there, too, because it can help to define what the appropriate assays may be and how to run them in multiplex forms, i.e., so that many suggested molecules can be run in parallel before doing more extensive experiments with a subset of the designs. But as anybody who has worked in the wet lab will tell you, cell-based assays are variable, and animal experiments even more so. Collecting the data from the actual experiments and refining things using AI tools is, of course, possible and is being done.

What it comes down to eventually is the quality of the data that is used for these AI approaches. The old adage of "crap in-crap out" still prevails. In the protein structure prediction space, there is enough data to be able to predict the three-dimensional structure of proteins at a resolution of about an angstrom, so predicted structures these days are pretty informative. AI

is also being adapted by many groups to look (for example) at VHH designs that interact with proteins in an epitope-specific way, complementing data from phage display or yeast display libraries. Unfortunately, data sets coming from cellular data are much less robust than protein structures, and it will take a while before AI can deliver equivalent results in this arena.

The approach is not cheap either. You tend to think that it costs you nothing to do a search on your computer. This is true, but these generative AI programs are at a very high-volume scale and use very considerable amounts of computational power and electricity. The costs of AI infrastructure add up very quickly.

The other area where AI tools are being extensively used is to search for information in scientific publications. It is almost impossible these days to keep up with what is published. Most weekly issues of *Nature* are now around 400 pages, so there is an increasing reliance on using AI to abstract the data and information you are looking for. The rub is that AI looks at information in a relatively unbiased way. Scientists do not. The quality of the information, what journal it got published in, who the authors are, and where they work are all part of the diligence that scientists use to judge the results of the experiments that were done and the conclusions drawn. AI does not have that capability. You can test this for yourself by doing a Google Gemini search or equivalent on something you know about and see what you get. It is generally rather superficial and sometimes just wrong.

At the time when DNA sequencing was all the rage and Celera was in full flow, some of the comments at the time were that there was more heat generated by the computers used to put all the fragments that were sequenced together than progress towards a full human genome sequence. The "hype heat" in the AI space presently is way more than the heat generated by all the processors that are being used to generate the data that the biotech and pharma companies are now going to be using.

Have I changed my mind? Maybe a little bit, but I do know that at the end of the day, the experiments that are done to test the designed molecules will be most important (and always will be) when you are making drugs for people. GEN

A-List Continued from page 11

Terns Pharmaceuticals
(NASDAQ: TERN)

At the American Society of Hematology (ASH) annual meeting in December, the small-molecule cancer drug developer presented what Andy T. Hsieh, PhD (William Blair) called unprecedented positive results for its oral, allosteric BCR-ABL inhibitor candidate TERN-701 in third-line or later chronic myeloid leukemia (CML): "We have increasing conviction that TERN-701 has the potential to effectively challenge [**Novartis**-marketed] Scemblix® [(asciminib)]'s market dominance across the CML disease spectrum" and its total addressable market of about $5 billion, Hsieh wrote in December, in a research note headlined in part: "Will TERN-701's differentiated Data Turn Into a Big Pharma Bidding War?" It's a question he suggested that can be answered in the affirmative: "We believe Terns' M&A prospect has increased considerably given the best-in-disease profile."

Travere Therapeutics
(NASDAQ: TVTX)

The rare disease drug developer generated talk from investors as a takeover target based on the expectation of quick FDA approval for its supplemental new drug application (sNDA) seeking to expand the label of Filspari® (sparsentan) to focal segmental glomerulosclerosis (FSGS) in addition to the current indication of adults with primary IgA nephropathy. Yet even after the FDA extended its review of Filspari to April 13, citing a "major amendment" to the sNDA from responses Travere furnished about the drug's clinical benefit in FSGS at the agency's request, Maury Raycroft, PhD, (Jefferies) still included the sNDA approval on his list of "events expected to occur or could occur through Q1'26"—resulting in "very high impact (>30%)" for the stock, which soared 77% in the six months ending February 11 based in part on the takeover talk.

Viking Therapeutics
(NASDAQ: VKTX)

Viking's development of VK2735, an obesity candidate that targets both glucagon-like peptide 1 GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, is far enough along at Phase III to earn the company a second consecutive year among *GEN's* top takeover targets. Another reason Viking should be attractive to would-be buyers is its valuation ($3.3 billion market cap), which one analyst considers a bargain: "We believe shares of Viking are significantly undervalued given the value attributed to **Metsera** ($10B final take-out bid) and the more advanced nature of Viking's obesity pipeline," Edward Nash (Canaccord Genuity) wrote in November. Data published in January from the Phase II VENTURE trial (NCT06068946) showed VK2735 treatment resulting in weight loss of up to 14.7% after 13 weeks. ■

References

1. Abivax also trades American Depositary Shares on NASDAQ under the same symbol, ABVX.
2. Inventiva also trades American Depositary Shares on NASDAQ under the same symbol, IVA.
3. Structure Therapeutics' shares traded on NASDAQ are American Depositary Shares.

Smarter Filings, Smarter Factories

How AI is uniting regulatory strategy and biomanufacturing

By Mike May

Artificial intelligence (AI) is no longer a futuristic add-on in the life sciences. It is rapidly becoming infrastructure. Across regulatory affairs and biomanufacturing, AI systems are moving from experimental pilots into validated, production-grade tools that directly influence how drugs are designed, manufactured, submitted, and approved.

Yet adoption has been cautious, and for good reason. Life sciences operate under some of the most stringent regulatory expectations of any industry. Accuracy, traceability, explainability, and validation are not optional. AI must earn trust not only from internal teams but also from regulators who ultimately decide whether a therapy reaches patients.

To understand how AI is being deployed responsibly across the drug lifecycle, *GEN* spoke with leaders from **Aizon**, **Clarivate**, **Ginkgo Bioworks**, and **IQVIA**. While their applications vary—from regulatory intelligence to factory-floor analytics to antibody design—a common theme emerges: AI's value depends not on autonomy, but on how well it augments human expertise within regulated systems.

Making regulatory affairs proactive

For IQVIA, the regulatory challenge is one of scale and fragmentation. Regulatory teams must manage expanding global requirements, frequent guideline updates, and massive volumes of documentation—all while maintaining precision and compliance.

Above. Tools based on artificial intelligence can be used to explore vast amounts of information and make use of it in regulatory and manufacturing applications across the biopharmaceutical industry. [Just_Super/ E+ / Getty Images]

"Regulatory information often resides in fragmented legacy systems, making analysis difficult," says Rachel Mercado, principal of AI consulting, clinical AI, and technology innovation at IQVIA. "At the same time, regulators require transparent, validated methods for confirming accuracy and reproducibility."

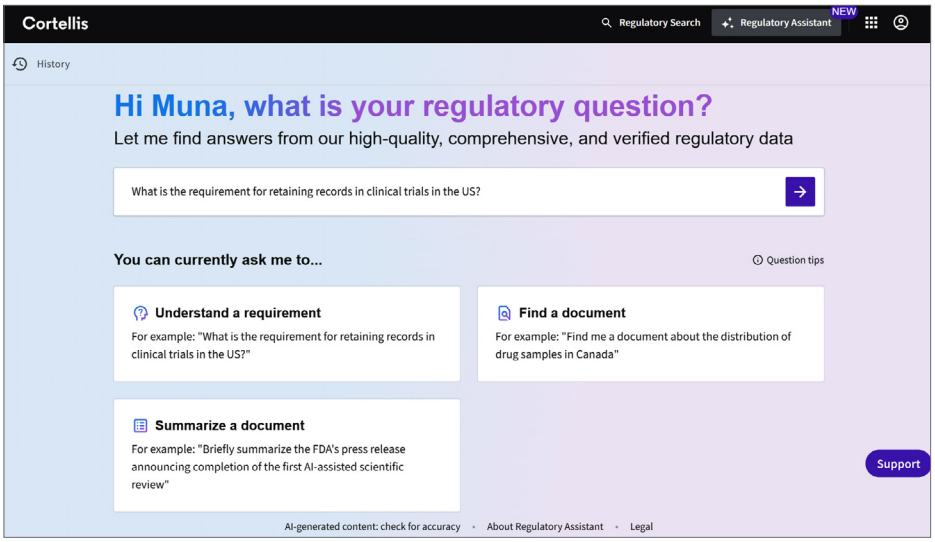
IQVIA's approach uses multiple forms of AI, each aligned to a specific regulatory function. Natural language processing (NLP)—a technology that allows computers to work with human language—extracts and classifies information from lengthy regulatory documents, identifying patterns, gaps, and anomalies that might otherwise be missed. Models based on machine learning (ML)—a branch of artificial intelligence where computers improve their performance by learning patterns from data instead of following fixed, hand-coded rules—add predictive capabilities, helping teams forecast approval timelines or flag risks for potential submission rejection.

On top of this foundation sit large language models (LLMs), which are advanced AI systems trained on vast amounts of text to understand context, generate coherent language, and perform a wide range of tasks, including predicting and reasoning. IQVIA uses LLMs to assist with summarization, drafting submission-ready narratives, and generating responses to regulatory queries. Knowledge graphs—structured networks of interconnected facts that represent entities and their relationships, enabling machines to reason about and retrieve information in a more human-like way—map relationships between regulatory requirements, products, and therapeutic areas, enabling semantic search and rapid impact analysis when guidelines change for a more proactive approach to regulatory submission strategies.

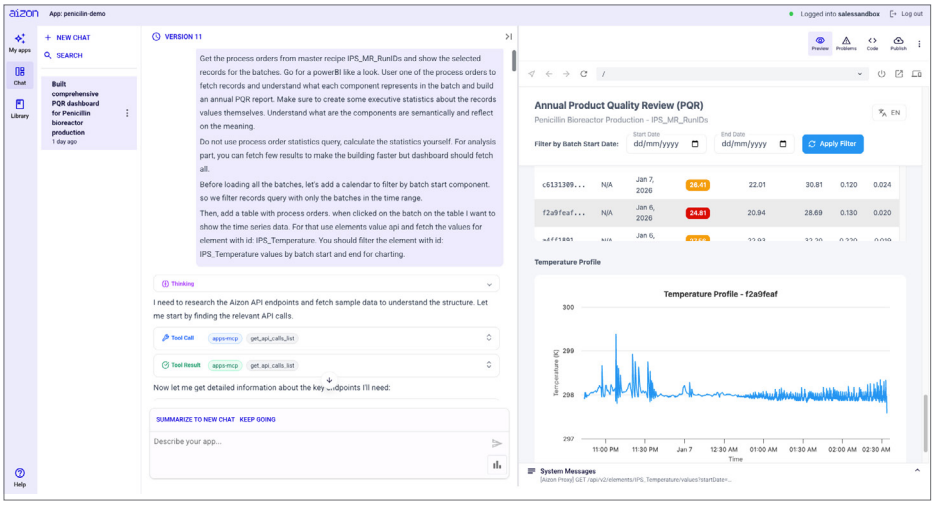
The most significant advance, however, is agentic AI, which consists of intelligent systems that can independently plan, make decisions, and take actions toward goals, adapting their behavior based on feedback from their environment. "Agentic AI enables dynamic, goal-driven coordination," says Raja Shankar, vice president, machine learning, clinical AI, and technology innovation, IQVIA. "It can gather information, draft submissions, review them for consistency and quality, monitor regulatory changes, and learn from past submissions."

Crucially, IQVIA emphasizes a human-in-the-loop model. "The promise of these solutions is not about replacing human expertise," Mercado notes, "but about strengthening their impact." Regulatory professionals remain accountable, with AI acting as a force multiplier rather than an autonomous decision-maker.

Looking ahead, IQVIA envisions agentic systems that augment the regulatory affairs function—maintaining regulatory intelligence, identifying potential risks early, and dynamically updating submissions as global requirements evolve. The result could be faster approvals across regions.



For regulatory workflows, an agentic-AI assistant can be used to find and understand guidelines or get information on requirements, as shown here. [Clarivate]



Agentic AI democratizes analytics. Here, a user of Aizon Agentic Studio enters a request in natural language (left) to build an Annual Product Quality Review (PQR), and the agentic AI instantly generates a dashboard (right) of information. [Aizon]

Building trustworthy AI

An additional challenge for leveraging AI for regulatory affairs is trust. For Yuval Kiselstein, vice president, R&D, life sciences, and healthcare at Clarivate, trust is the gating factor for adoption.

"One of the primary challenges is ensuring accuracy and trustworthiness," he says. "AI hallucinations or unverified outputs can introduce significant compliance risks in regulated filings."

Clarivate addresses this through a tightly controlled architecture that combines commercially pretrained LLMs with domain-specific regulatory layers. A crucial component is retrieval augmented generation (RAG), which ensures that AI-generated responses are grounded exclusively in curated regulatory content. "This significantly reduces the risk of hallucinations," Kiselstein explains, "and ensures alignment with current guidance and requirements."

Transparency is equally important. Regulatory professionals must be able to trace every answer back to authoritative source documents. Without that traceability, AI outputs cannot be confidently used in submissions, audits, or interactions with health authorities.

Clarivate's latest advance is an agentic AI assistant designed specifically for regulatory workflows. Rather than simply retrieving documents, the assistant supports conversational search, comparative analysis of guideline versions, and alerts related to regulatory changes.

"The assistant helps users identify what's relevant, understand the implications, and determine next steps," Kiselstein says. "It operates exclusively on high-quality, trusted regulatory content."

The benefits include faster research, improved confidence in decision-making, and a clearer understanding of how regulatory changes affect active or planned submissions. Multilingual capabilities further enable global teams to access regulatory intelligence without delays.

> **AI hallucinations or unvarified outputs can introduce significant compliance risks in regulated filings.**
>
> —Yuval Kiselstein, VP, R&D, Life Sciences, and Healthcare, Clarivate

Clarivate envisions its multi-agent AI solution as a trusted partner to regulatory experts, enhancing decision-making by identifying gaps, anticipating challenges, preparing critical submission materials, and strengthening inspection readiness."

Making manufacturing AI-compliant

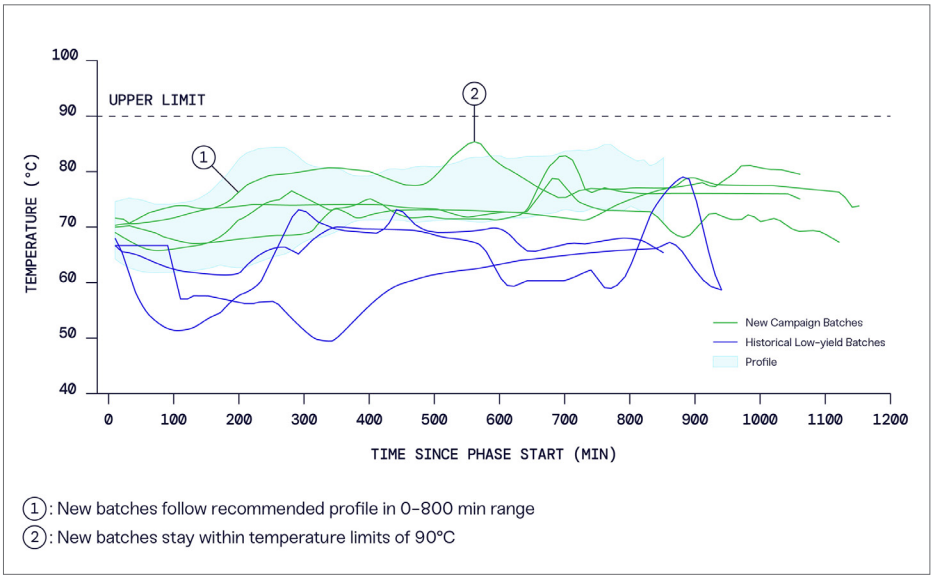
If regulatory AI lives in documents and databases, manufacturing AI lives on the shop floor. For Aizon, the challenge is not a lack of data but a lack of usable, contextualized, and unsiloed data.

"Artificial intelligence runs on data, and biomanufacturing generates massive amounts of it," says Toni Manzano, PhD, co-founder and chief scientific officer of Aizon. "But it's often siloed and lacks context."

A temperature spike, for example, is meaningless unless the AI knows which batch, which phase, and which equipment state was active. Compounding the problem, many manufacturing processes are still partially manual, requiring digitization before AI can even be applied.

Aizon Predict, the company's AI governance platform, blends several AI disciplines. Supervised and unsupervised ML models predict critical quality attributes and yield outcomes before a batch is finished, enabling real-time process adjustments. Digital twins interact with biological processes, such as upstream and downstream operations, allowing the process to adapt to the inherent variability of biomanufacturing to always obtain a perfect batch.

Aizon has also embraced agentic AI, integrating LLMs into applications and analytics, introducing the control mechanisms recommended by good manufacturing practices (GMP). The result is a conversational interface that replaces



An AI-powered batch comparison of temperature profiles during a critical process phase detects deviations, such as early temperature rise (1) and transient overshoot (2), which are potential indicators of batch performance issues. [Aizon]

static dashboards.

"A quality director can ask, 'Show me the yield trend for product X over the last six months and correlate it with pH deviations,'" Manzano says. "The system generates the analysis, charts, and report, which are then ready to be reviewed by the subject-matter expert."

This shift dramatically accelerates insight generation, democratizes advanced analytics, and speeds creation of regulatory documentation such as product quality reviews and root cause analyses. Importantly, explainability and validation remain central—black-box AI has no place in GMP environments.

Manzano's long-term vision is real-time release, where AI provides sufficient statistical assurance to release a batch immediately upon completion. For personalized therapies like cell and gene treatments, such capabilities could be transformative.

Developability by design

At **Ginkgo Bioworks**, AI is applied even earlier—during molecule design. The focus is on antibody developability: the likelihood that a promising molecule can be manufactured, formulated, and delivered successfully at scale.

"The central challenge is data," says Rich Cohen, PhD, senior director, Ginkgo Datapoints, and Ammar Arsiwala, PhD, director of antibody development, Ginkgo Bioworks. Public developability datasets are limited in size, standardization, and metadata quality, making it difficult to build generalizable predictive models.

Ginkgo addresses this by generating high-throughput datasets for pharma customers, spanning hundreds to thousands of antibodies across multiple assays. Those customers, often in collaboration with Ginkgo, build ML models to predict developability properties directly from sequence for future drug discovery campaigns. Ginkgo also uses generative AI, which is a class of artificial intelligence that creates new content—such as text, images, code, or audio—by learning patterns from existing data and producing original outputs that resemble what it has learned. Ginkgo scientists use generative AI to design new antibody variants with targeted developability properties. "In our most recent wet-lab tested designs, we're seeing good ability to tune properties in both directions," Cohen and Arsiwala say.

Beyond internal modeling, Ginkgo is pushing industry-wide standardization. Through the Antibody Developability Competition, which was hosted by Ginkgo, and the Antibody Developability Consortium, which was created through a partnership between computing-platform maker **Apheris** and Ginkgo Datapoints, Ginkgo aims to establish shared benchmarks, standardized assays, and federated models trained across partners.

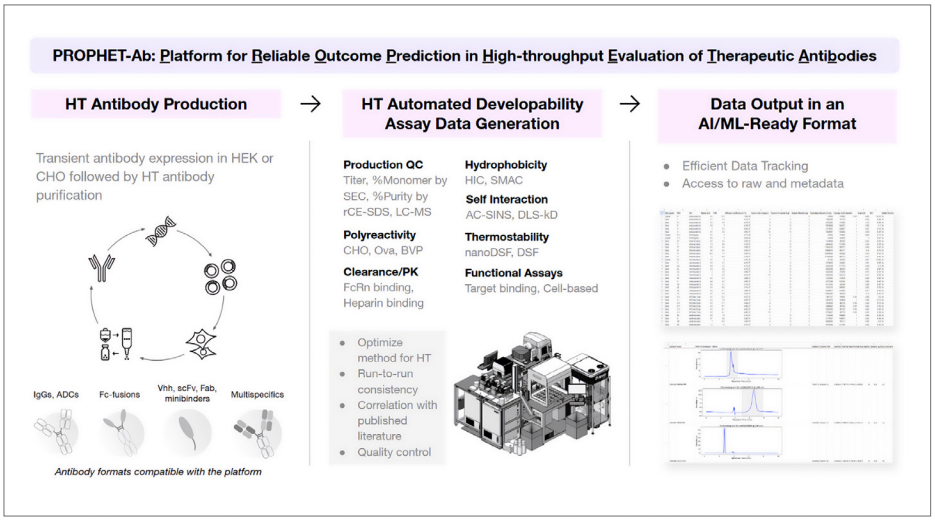
> **For AI, the challenge is not a lack of data but a lack of usable, contextualized, and unsiloed data.**

The goal is to improve the predictability of real-world outcomes, from manufacturability and stability to device interactions and clinical performance. As therapies become more complex—particularly multispecific antibodies—AI-driven design may be essential to making them manufacturable at all.

Converging on smarter and faster

Across regulatory affairs, manufacturing, and developability, a clear pattern is emerging. AI is not replacing human judgment—it is compressing timelines, surfacing insights, and connecting data across silos that once slowed drug development.

The future of AI in life sciences will not be defined by autonomy, but by trust. Systems that are explainable, validated, and grounded in high-quality data will move from support tools to strategic infrastructure. And as these capabilities mature, the ultimate beneficiaries will be patients—who gain faster access to safe, effective medicines built for approval from the very beginning. GEN



To design therapeutic antibodies that can be successfully manufactured, Ginkgo Bioworks incorporates many tools, including AI and ML. [Ginkgo Bioworks]

Genome Editing for **Biopharmaceutical Manufacturing**

By Surya Karunakaran, PhD, and Ferenc Boldog, PhD

Accelerating biologics through the synergy of synthetic biology and genome engineering

Surya Karunakaran, PhD
Director, Product Management, ATUM

Ferenc Boldog, PhD
Director Emeritus, Cell Line Development, ATUM

Chinese Hamster Ovary (CHO) cells have been the industrial workhorse for production of biopharmaceuticals since the 1980s, with the first CHO-derived product approved by the FDA in 1987. Nearly five decades later, CHO cells are the primary mammalian host for biopharmaceutical manufacturing due to their ease of manipulation, robust growth in high-density suspension cultures and post-translational modification machinery that yields human-compatible glycosylation profiles. The increasing complexity of next-generation biologics such as bi- and trispecific antibodies, antibody-drug conjugates (ADCs), and vaccines demands novel, enabling technologies for CHO genome engineering.

While tools like CRISPR-Cas9, Transcription Activator-Like Effector Nucleases (TALENs), and Zinc-Finger nucleases (ZFNs) have demonstrated great utility, primarily for genetic knock-out applications, none have been adopted as widely for biopharmaceutical manufacturing as transposases. Since their discovery by Nobel laureate Barbara McClintock, transposase/transposon pairs (jumping genes) have profoundly changed how we perceive genomic fluidity and structural integrity. Recent efforts in the development of hyperactive transposase systems coupled with synthetic biology have created a single, efficient tool for genetic knock-ins, knock-downs, and for complex bioengineering needs. Transposases are fundamentally altering the paradigm of CHO-cell engineering.

Limits of traditional gene editing

Early strategies for site-specific integration relied on homologous recombination driven by extensive homology between the recombinant sequence and its genomic target.[1] Homologous recombination is a rare event in mammalian cells, occurring with a frequency of approximately 1 in 10^6-10^7 cells per generation. Moreover, CHO cells are particularly recalcitrant to homology dependent repair (HDR), which makes this approach unviable for CHO engineering.

Another approach involves the engineering of "landing pads" with recombinase recognition sequences at genomic hotspots. Upon expression of the recombinase enzymes (Cre, FLIP or ΦC31), donor plasmids containing FRT, Lox, or attP/attB sequences can be site-specifically integrated via recombinase-mediated cassette exchange (RMCE). While conceptually elegant, this is a labor-intensive process. It requires the creation of the cell line with the landing pad, followed by recombinase mediated cassette exchange to generate the recombinant cell line. This approach also requires extensive screening for transcriptional hot spots, which is not trivial. The levels of productivity afforded by a single transgene copy were also rarely viable for biomanufacturing.

Targeted nucleases like CRISPR-Cas9, TALENs, and ZFNs sought to address these limitations by inducing site-specific double-strand breaks (DSBs) at defined genomic loci. However, non-homologous end joining (NHEJ), which is the dominant repair pathway in mammalian cells, quickly ligates broken DNA ends, resulting in insertions or deletions. While well-suited for gene knockout, this is detrimental for precise gene insertion.[2] Homology-directed repair (HDR) pathway, required for template-guided, precise gene knock-in, is significantly less active and restricted primarily to the S and G2 phases of the cell cycle. This leads to low insertion efficiencies in industrially relevant CHO cells (estimated to be around 1 in 100,000), requiring the need for selection mechanisms or

high-throughput screening methods to find the appropriate clones. This efficiency disparity has largely limited the utility of the targeted nucleases for applications that require integration of expression cassettes or other genetic elements.

An attractive solution to overcome the inefficiency of the HDR mechanism is to associate the DNA-binding domains of targeted nucleases with transposase enzymes. For instance, researchers have fused catalytically dead Cas9 (dCas9) with piggyBac transposase to accomplish site-directed transposition. This "chimeric transposase" approach combines targeting capabilities with high-efficiency transposition and has high potential to streamline site-specific modifications in CHO cells.

Key features of transposase systems

Transposon systems, such as the widely employed Leap-In Transposase® and piggyBac transposase, overcome the limitations of NHEJ-dependent repair by facilitating enzyme-catalyzed, semi-targeted "cut-and-paste" integration of a transgene cassette into the host genome. In contrast to RMCE and targeted nucleases, transposases offer two critical advantages: multi-copy integrations across the CHO genome and high transposition efficiency, resulting in highly productive homogeneous cell populations.

The transposase enzyme typically requires only a short target sequence (e.g., TTAA) and an open chromatin region, resulting in anywhere between 2 and 50 integration copies per CHO genome.[3] The integrity of the transposed DNA is stably maintained at every integration site, resulting in high-titer stable cell lines with exceptional genetic stability.[3] Furthermore, transposases promote highly efficient transposition even for large cargo sizes approaching 10–20 kb.

This mechanism generates stable, homogenous cell pools where most clones have high productivity and product quality attributes that closely resemble the original pool. These stable pools have been used to accelerate the transition from discovery to early stage manufacturing. During the COVID-19 pandemic, several organizations utilized transposase-derived pools for IND-enabling studies and for early manufacturing slots, suggesting a future where CHO-derived recombinant biopharmaceuticals could be brought to market a year faster than is possible today, saving lives and reducing drug development costs.

Synthetic biology, modular vectors

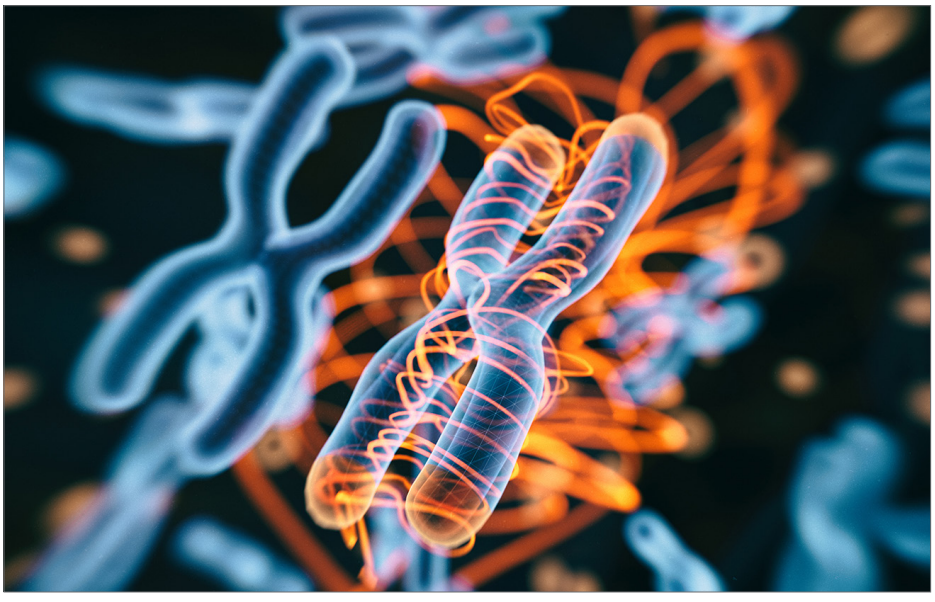
The rapid adoption of transposases is in part due to the application of synthetic biology (Synbio) principles, specifically the Design-Build-Test-Learn (DBTL) cycle, to engineer hyperactive transposase variants that exhibit significantly enhanced transposition efficiency. Leading technology platforms have paired these advances with the development of modular expression vector architectures and cloning tools to rapidly test and build a library of genetic elements (promoters, untranslated regions, polyadenylation signals, selection marker cassettes) to optimize the expression of any given biologic architecture.

This marriage of synthetic biology and protein engineering empowers the commercialization of complex biologics by providing a toolbox to refine transposon design in early research while creating a robust workflow for stable cell line generation. Recent publications[4,5] report the generation of high-titer stable cell lines for expression of complex 4-chain bispecifics, protein-nanoparticle vaccines, and trispecific T cell engagers, all of which required an early screen of transposon vector design to optimize chain ratios, expression, and critical quality attributes (CQAs).

Advanced CHO engineering

The most sophisticated application of transposon technology lies in the serial engineering of the CHO host using orthogonal transposase enzymes. These enzymes, derived from different species, recognize distinct inverted terminal repeats (ITRs) and do not cross-mobilize or interfere with previously inserted expression cassettes.[6] Orthogonal transposase-transposon pairs open the door to multiplexing genome engineering, where simultaneous sequence knock-in and/or functional knock-down is performed either serially or in parallel.

See Thought Leader continued on page 24



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Pharma's AI Investment

Signals New Drug Discovery Paradigm

By Fay Lin, PhD

Therapeutic developers are increasingly rebuilding their workflows around AI to bring drugs to patients faster

From improved molecular design to AI-driven automation, waves of AI tools promise to accelerate therapeutic development. Still, skeptics ask whether this momentum reflects real transformation or simply hype in drug discovery.

Mike Nally, CEO of **Generate:Biomedicines**, emphasizes that the promise of AI lies in delivering better medicines to patients faster. What is typically a 10–15-year journey from discovery to clinical approval, he says, could potentially be compressed into an eight-year paradigm with AI technologies.

Founded in 2018, the Flagship Pioneering company recently completed one of the industry's largest IPOs in years, raising $400 million in gross proceeds toward clinical trials and R&D efforts. Generate's AI platform includes an optimization stack guided by existing molecules, and a second layer that designs proteins from scratch.

Generate's optimization approach gives machine learning models an existing therapeutic binder as a starting point. Researchers then computationally learn the functional landscape to improve the molecule for clinical drug properties. The company's current workflows can complete optimization rounds within a couple of weeks, while three rounds of design optimization, on average, are sufficient to reach the desired criteria.

Nally tempers that new computational tools are not a panacea for every part of drug development.

"If you pick the wrong target, dose, or patient population, no technology will overcome those things," he said. "If you have a transformational technology, you have to first prove the technology works in the clinic."

In December, Generate announced that its most advanced program, GB-0895, an anti-thymic stromal lymphopoietin (TSLP) antibody for severe asthma, entered Phase III clinical trials. GB-0895 is the first "AI-derived" antibody to reach this clinical milestone, progressing from discovery to Phase III within five years. The two global studies, SOLAIRIA-1 and SOLAIRIA-2, will evaluate GB-0895 in approximately 1,600 adults and adolescents with severe asthma.

More shots on goal

In preclinical discovery, researchers grapple with identifying the right molecule to advance to the clinic. AI promises to accelerate multiple stages of the pipeline—from target discovery and molecular design to clinical validation.

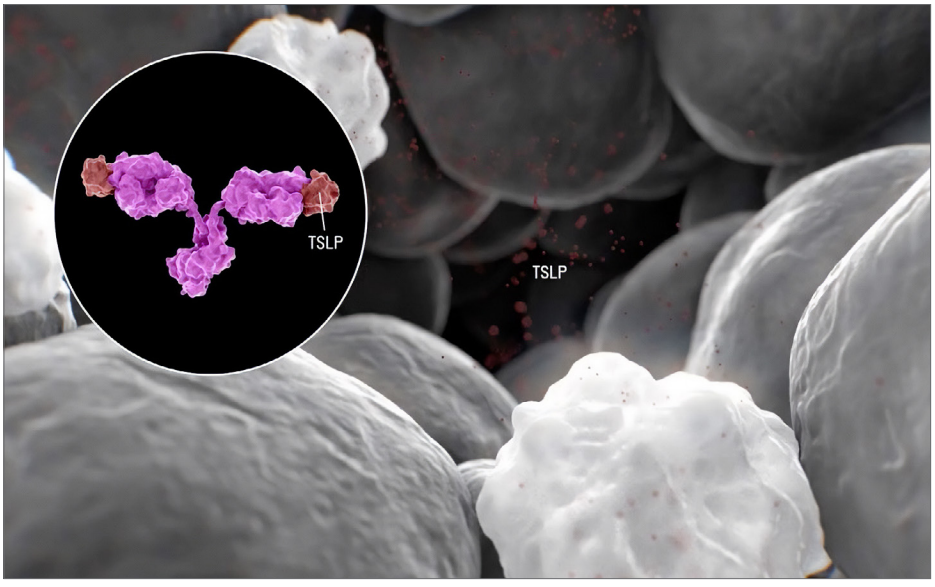
"Have we seen a big impact yet? We are still not there, especially on the research side," said Sai Jasti, SVP, head of data science and AI at **Bayer**, when describing the role of AI platforms. He says Bayer has an internal goal to increase R&D productivity by 40% in 2030.

To achieve this aim, Bayer has entered a three-year strategic collaboration with **Cradle**, an AI-based protein design company, to accelerate protein optimization across Bayer's therapeutic antibody pipeline. By reducing the number of optimization cycles and improving developability properties, including potency, safety, and manufacturability, Cradle's platform will expand Bayer's biologics portfolio.

Anastasia Hager, PhD, head of drug discovery sciences, SVP, pharma R&D at Bayer, says the company has been on a journey to replenish its early pipeline given growth across multiple indications, including cardiovascular, immunology, oncology, and neurodegenerative disease.

"The most exciting piece is enabling creativity to test different sequences while unlocking target and structural space," said Hager when describing the value-add

Left. Researchers examining tumor tissue sections. Bayer researchers develop solutions in response to challenges in healthcare. [Bayer]



GB-0895, an anti-TSLP antibody for severe asthma, is the first "AI-derived" antibody to enter Phase III clinical trials. [Generate:Biomedicines]

of Cradle's platform. "We're committed to enhancing our pipeline with data science and AI as key tools for the biologics portfolio."

When moving molecules through the clinic, Stef van Grieken, co-founder and CEO at Cradle, says translation is not a solved problem. Yet, the ability to more quickly identify candidates early in the development pipeline while increasing biological understanding of the target will "provide more shots on goal" to support informed decisions during drug development.

In that vein, Jasti emphasizes that the partnership is "not just a software deal," but a collaboration on the scientific and machine learning level, where scientists from both organizations will exchange ideas and expertise on research direction. Cradle's platform will also be embedded in Bayer's workflows to improve accessibility for scientists in the lab.

Year of deployment

While traditional tech-pharma collaborations focus on a small number of drug targets, 2026 kicked off with a stream of AI platform deals across pharma, signaling a cultural shift of investing in AI infrastructure for broad discovery.

"If 2025 was the year of breakthrough research, we believe 2026 will become the year of deployment," said Jack Dent, co-founder at **Chai Discovery**, an AI-driven biologics company developing therapeutics against undruggable targets.

Chai's core technology centers on Chai-2, a *de novo* antibody design model capable of generating full-length antibodies with therapeutic attributes. The model speeds up workflows by reducing reliance on labor-intensive and time-consuming experimental screens.

Earlier this year, Chai announced a collaboration with **Eli Lilly** to deploy Chai's technology to design novel biologics for multiple targets. Chai will also develop an exclusive AI model for Lilly that is trained on the pharma giant's proprietary data and tailored to Lilly's discovery workflows.

According to Aliza Apple, PhD, vice president of Lilly Catalyze360 AI/ML and global head of Lilly TuneLab, Lilly's tech philosophy centers on being an early adopter of promising tools. She emphasizes that models must be trained on quality data and undergo rigorous testing to design better molecules.

"We want to lean in early to the tools that look truly differentiated and put Lilly's weight behind them, not just rely on what we've already built," said Apple. Rather than outsourcing therapeutic design, the collaboration with Chai gives Lilly scientists direct access to Chai's generative AI capabilities.

From molecules to humans

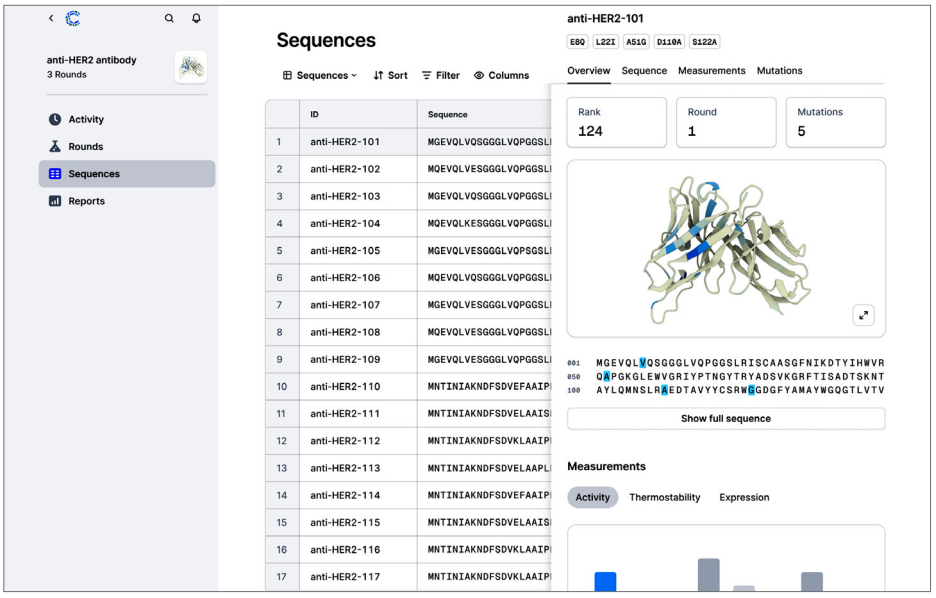
Other biotechs have focused their efforts entirely on building platforms, rather than developing drugs internally. **Boltz**, an AI research and product company, launched in January with $28 million, with a mission to advance open science for drug discovery.

The public benefit corporation (PBC) is co-founded by MIT researchers—Gabriele Corso, PhD, Jeremy Wohlwend, PhD, and Saro Passaro, known as the developers of the widely adopted Boltz series of models. The Boltz team first made waves in November 2024, with the launch of the co-folding model, Boltz-1, a fully commercially available AI model to achieve AlphaFold 3-level accuracy in predicting the 3D structure of biomolecular complexes.

Boltz has already solidified a multi-year collaboration with **Pfizer** to build exclusive models that improve target selection for structure prediction, small-molecule affinity, and biologics design. Boltz scientists will also build custom models and workflows with Pfizer for a number of target programs to enhance preclinical decision-making.

Corso, who leads Boltz as CEO, said two realizations drove the decision to turn the Boltz models into an enterprise.

"First, continuing to push the frontier of biomolecular AI requires sustained investment in talent, compute, and data



Cradle platform users can view detailed information about their generated sequences. The platform also provides an overview of user design strategy and configurations, and access to generation reports and round results to move protein engineering projects forward more efficiently. [Cradle]

FROM DISCOVERY TO LOT RELEASE:

A Validated Suite of Assays for Biologics Drug Development

An integrated suite of bioassays provides a coherent workflow to track antibody Fc effector activity across every stage of mAb drug development

Potency assays that fail during tech transfer or comparability studies don't just delay timelines—they erode regulatory confidence and cost development cycles. Advancing drug candidates and maintaining product quality post-approval requires functional evidence of a drug's activity, potency, and mechanism of action (MoA) using validated assays for QC and lot release to ensure batch-to-batch consistency, safety, and compliance.

Effective against a variety of diseases, therapeutic antibodies and Fc fusion proteins have exquisite specificity in binding to an antigen, and the ability to activate an immune response through Fc effector functions like antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

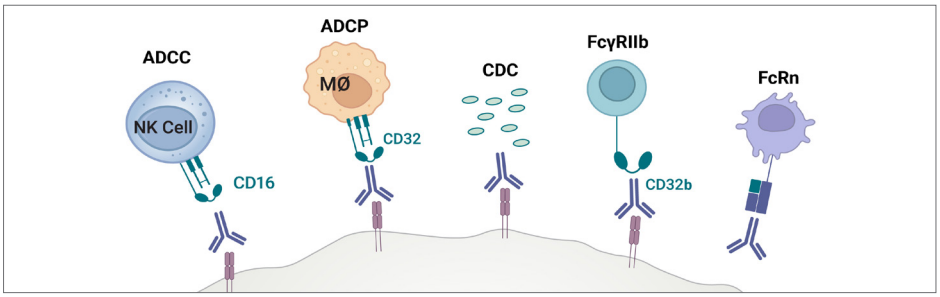
Promega's comprehensive assay suite provides a coherent workflow that tracks antibody Fc effector activity from binding to function. To provide greater control and confidence in Fc analytics, the bioluminescent assays adhere to ICH Q2(R2) guidelines and robustly and efficiently measure Fc effector functions across antibody development pipelines from early-stage discovery through commercial production and lot release.

The assays combine biological relevance with reproducibility while eliminating labor-intensive protocols, are scalable, and deliver decision-ready data that meet regulatory guidelines. The suite includes Lumit® FcγR Binding Immunoassays, Lumit C1q Binding Assay for CDC (Complement-Dependent Cytotoxicity), Fc Effector Reporter Bioassays for ADCC and ADCP and HiBiT Target Cell Killing Bioassays using MoA-qualified primary cells.

Screening and Ranking Candidates

During the early antibody discovery process, Lumit® FcγR Binding Immunoassays provide fast, reliable data to screen candidate binding kinetics and rank order IgG isotypes based on their affinity to the different Fcγ receptors on immune effector cells.

The add-mix-read immunoassays include all major Fcγ receptor subclasses known to be present on human effector cells including FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, and FcγRIIIb, as well as FcRn. The suite includes the allelic variants for FcγRIIa-H131 and -R131 and FcγRIIIa- V158 and -F158. Together, these receptors cover phagocytic, cytotoxic, and inhibitory immune functions.



Promega

An integrated suite of bioassays covers the full spectrum of antibody Fc effector functions from ADCC, ADCP to CDC and receptor binding by providing a coherent workflow to track monoclonal antibody activity from early development through commercial lot release.

These assays generate a luminescent readout with results available in < 60 min without immobilization artifacts, enabling 96- to 384-well high-throughput primary screens or orthogonal confirmation.

To accurately detect specificity and sensitivity across antibody variants through CDC, the Lumit® C1q Binding Assay is based on a split luciferase technology—half of the luciferase (LgBiT) is bound to C1q and half is bound to anti-IgG Fab tracer (SmBiT). A luminescent signal is generated only when the labelled C1q and an anti-IgG Fab tracer are brought into close vicinity by the test antibody, forming an active NanoBiT luciferase through complement binding.

Measuring Receptor Activation

Functional Fc Effector Reporter Bioassays directly measure Fcγ receptor activation. They employ thaw-and-use target and reporter cells expressing individual human FcγRs to provide ICH-compliant precision, accuracy, and linearity for identifying Fc binding changes that translate into functional potency shifts.

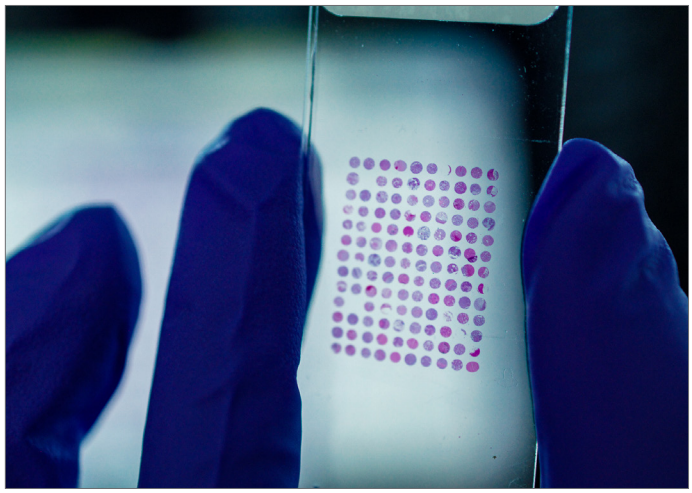
When co-cultured with an IgG antibody, the FcγR is activated and triggers promoter-driven luminescence that is detected using the Bio-Glo™ Luciferase Assay System. The add-mix-read format standardizes reagents to eliminate donor-to-donor variability and reduce background signals.

The ADCC Bioassay reflects the MoA and specificity of antibodies designed to bind and activate FcγRIIIa while demonstrating appropriate isotype specificity. The ADCP Bioassay reflects the MoA and specificity of antibodies designed to bind and activate FcγRIIa.

HiBiT Target Cell Killing Bioassays can be used to measure cytotoxic target cell killing induced by a variety of drug modalities, including validation of Fc effector function. The HiBiT TCK Bioassay pairs MoA-qualified thaw-and-use primary effector cells, including PBMCs for ADCC and macrophages for ADCP activity to reduce variability.

The bioassay features a complementation luciferase technology, where upon killing of the target cell, the HiBiT fusion protein is released into the media and binds extracellular LgBiT to create a functional luciferase enzyme. Cell death of the target cell confirms primary PBMC or macrophage activity, providing quantitative, no-wash cytotoxicity readouts that bridge binding and reporter potency data to physiologic cell death.

The integrated suite of assays provides a coherent workflow that tracks antibody Fc effector activity from initial screening through lot release. Accelerate IND and BLA filings with assays that arrive validation-ready—and stay compliant from first candidate to final lot release. Assays contain system-suitability controls, defined acceptance criteria, and lot-specific documentation, facilitating incorporation into comparability, stability, and release protocols. ■



Noetik generates multimodal data from primary human tissue samples with intact *in vivo* context. These data train biological foundation models that can predict cancer clinical outcomes. [Noetik]

at a scale not attainable within academic environments," Corso explained. "Second, truly democratizing the technology, and maximizing its impact, means going beyond publishing models and building reliable, well-designed products that scientists could integrate directly into their daily work."

While much of the industry is focused on molecular design, San Francisco-based **Noetik** is building biological foundation models trained on human data.

Ron Alfa, MD, PhD, CEO of Noetik, emphasizes that a huge gap remains for large-scale translational data, preventing drugs from succeeding in the clinic. As an answer, the company generates multimodal data from human tissue samples with an intact *in vivo* context. These data fuel Noetik's foundation models, which predict clinical outcomes in cancer.

Earlier this month, Noetik announced a five-year licensing partnership with **GSK**, which gives the pharma giant access to Noetik's non-small cell lung cancer and colorectal cancer models. The deal includes a $50-million upfront payment and will follow a subscription-based framework.

Alfa describes the GSK partnership as one of the first true foundation model licensing deals in biotech. "For years, the sector has looked for a way to commercialize AI as infrastructure rather than the standard R&D collaborations," he said. "Now, we have a template."

Whether AI-driven drug discovery is reality or hype, rising pharmaceutical investment points to the former. The ultimate payoff, however, will be decided in the clinic. GEN

Thought Leader

Continued from page 19

The intrinsic stability of transposon-integrated elements enables consistent 1-to-1 transfer of information from the experimental design to the genome of the CHO cell, the so-called "what you see is what you get" of biotechnology. Transposon-mediated genome engineering is almost entirely devoid of gene concatemers, truncations, duplications, and other non-designed genome recombination, making genome engineering a more predictable science.

Orthogonal transposases are already used to rapidly establish bespoke host cell lines for product-specific applications. The original CHO host can be engineered to overexpress key glycosyltransferases or to knock down endogenous CHO enzymes (e.g. FUT8) to pre-program glycosylation characteristics. Subsequently introducing the target protein using a second orthogonal transposase will not interfere with the already integrated modifications. Alternatively, an existing antibody-expressing cell line can be retrofitted with glycan modifying enzymes on a second orthogonal transposon without impacting existing integration sites.

Modular vectors and orthogonal transposases also enable the engineering or enhancement of entire metabolic pathways. For example, improving sialylation of therapeutic proteins requires the coordinated overexpression of multiple enzymes, such as the sialic-acid substrate-generating enzyme GNE, along with B4GALT1 (galactosyltransferase) and ST6GAL1 (sialyltransferase). The expression level of each enzyme in this cascade can be fine-tuned in the transposon vector, and complex pathways can be engineered with the help of orthogonal transposase enzymes.

In summary, transposase technology has matured over the last 10 years from a simple integration method into a scalable, widely applicable, genetic engineering tool used by companies developing biopharmaceuticals. By enabling stable, multi-copy integrations through hyperactive enzymes and leveraging synthetic biology principles in transposon vector design, it allows for quick testing and refinements for new complex biologic formats early in preclinical stages and for the establishment of robust, scalable processes for stable cell line generation. Both features have encouraged wide adoption and application of the transposase technology in the field of biopharmaceutical development. GEN

Surya Karunakaran, PhD, is the director of product management at ATUM. Ferenc Boldog, PhD, is director emeritus, cell line development at ATUM.

References available online.

SPOTLIGHT

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Welcome to **GEN Spotlight**—a 2.5 hour virtual event on the dynamic field of **Organoids**.

In this inaugural **GEN Spotlight** on Organoids, hosted by Deputy Editor in Chief Julianna LeMieux, PhD, we are delighted to feature a fireside chat with renowned stem cell pioneer and organoid researcher **Hans Clevers, MD, PhD,** of the Hubrecht Institute in the Netherlands. The GEN Spotlight will also feature a roundtable discussion with leading researchers, a presentation from an industry thought leader, and a breakout session from one of our sponsors.

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Redesigning Tomorrow's Crops

By Kathy Liszewski

As climate pressure mounts, new platforms tackle delivery, regulation, trait stacking, and data bottlenecks limiting agricultural genome editing

Climate change, population growth, and mounting pressures from plant diseases are helping drive a global food crisis. Reliable crop production is becoming increasingly challenging, exposing the limits of conventional crop improvement, and fueling demands for more precise solutions. While CRISPR-based genome editing represents a powerful tool for enhancing crop resilience, yield stability, and sustainability, its use is still evolving. Many agricultural biotechnology (AgBio) scientists are advancing the technology while also confronting key issues such as delivery constraints, biological complexity, long development timelines, cost, and public acceptance.

Industry innovators are meeting at the *8th Annual CRISPR AgBio Congress* (March 23–25) to discuss the next generation of plant genome engineering. Featured approaches include viral delivery systems that bypass tissue culture, systematic optimization of promoters and coding regions for enhancing complex traits, precision editing breakthroughs such as non-browning bananas, multiplex editing platforms that accelerate trait stacking, and AI-driven frameworks that convert vast biological datasets into actionable trait targets.

Climate-resilient crop traits

Although CRISPR-based genome editing offers a promising tool for engineering stronger, more resilient crops, its agricultural application faces technical hurdles and crop-specific constraints. "The molecular size of first-generation CRISPR tools like the Cas9 limits their use with viral vectors," reports Shira Corem, PhD, vice president of R&D at **BetterSeeds**. "CRISPR's use in agriculture is also limited by heavy reliance on tissue culture and regeneration, long development timelines, and high costs."

Corem says the company has developed a technology that aims to broaden the application of CRISPR. "Our EDGE™ (Efficient Delivery of Genome Editing) platform uses engineered plant viruses to deliver next-generation small genome-editing components directly into plant cells. Viral delivery enables highly efficient systemic expression of editing machinery, which is critical for achieving edits without the need for specific, long, and laborious tissue culture and regeneration procedures, dramatically shortening timelines and reducing costs."

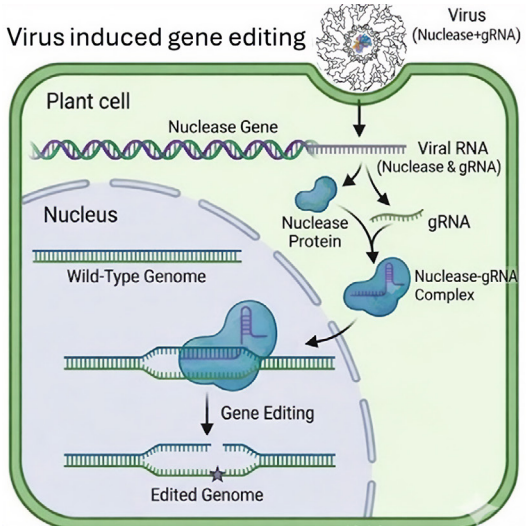
According to Corem, BetterSeeds also provides a portfolio of small, highly active, and cost-efficient nucleases that are particularly well suited for viral delivery. She elucidates, "Their compact size enables efficient packaging and higher viral genome stability, supporting robust editing performance. This combination significantly expands the range of crops and tissues that can be edited."

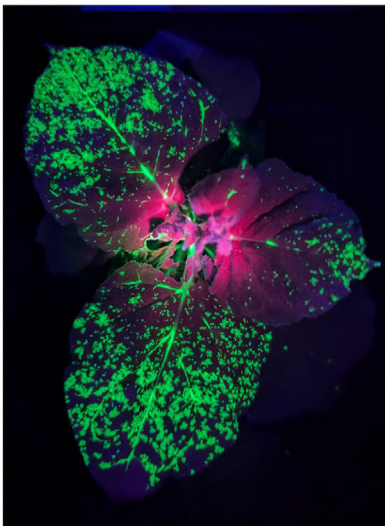
To better enable rapid deployment, the company also provides access to a validated set of robustly applicable climate-resilience genes that allow rapid deployment of traits such as stress tolerance, improved yield stability, disease resistance, and environmental adaptability.

Corem believes gene-edited crops will be essential for addressing climate change, food security, and sustainability. "We aim to democratize genome editing so it is no longer limited to a small number of crops, companies, or regions, but can be used by all breeders, researchers, and farmers worldwide."

Optimizing promoter and coding regions

For many agronomic traits, gene editing strategies based solely on gene knockouts fail to deliver meaningful improvements, according to Dror Shalitin, PhD, founder and CEO of **PlantArcBio**. "Instead, traits often require precise optimization of gene regulation and/or gene





Left side – EDGE™ by BetterSeeds aims to overcome viral cargo constraints by delivering both the nuclease and guide RNA using viral vectors, enabling assembly of a complete CRISPR system directly in wild-type plants and allowing the practical use of multi-kilobase cargos. *Right* – To visualize gene editing in real time, LIVE-EDGE™ utilizes a unique green fluorescent protein (GFP)-based reporter in which targeted editing activates GFP expression. [BetterSeeds]

Left. Bananas rank as a globally important fruit yet suffer from post-harvest browning. Using its GEiGS genome-editing platform, Tropic Biosciences has introduced precise genomic modifications to develop a non-browning banana. [Tropic Biosciences]

function, through targeted modification of promoters and/or coding regions, to enhance expression levels, expression patterns, or protein performance."

Shalitin says a key challenge, though, is the "lack of a systematic, high-throughput way to test and identify the exact regulatory or coding changes required directly in plants and under relevant biological conditions. Without such capability, unlocking the full potential of gene editing for complex traits remains limited."

To help solve this bottleneck, the company has developed its DIP™ and DIPPER™ platforms for gene discovery and gene editing, respectively. Shalitin explains that "DIP is a powerful, high-throughput in-plant discovery platform designed to identify novel genes from nature that enhance crop performance through gene introduction. By screening millions of genes directly in plants, under relevant growth and stress conditions, DIP identifies the best-performing genes for traits such as yield improvement and drought tolerance, with strong and reproducible results already demonstrated in crops including corn."

On the other hand, the DIPPER platform enables systematic in-plant optimization of gene regulation and gene function through screening of promoter and coding-region variants. Shalitin continues, "Promoter variant screening enables identification of optimal expression levels required for a given trait. This is particularly important for traits such as drought tolerance or other abiotic stress tolerance, and traits such as herbicide tolerance, nutrition improvement, and disease resistance, where over- or under-expression can reduce performance. Systematic screening allows selection of precise regulatory variants that maximize trait performance."

Shalitin says a key advantage of the company's approach is the ability to de-risk gene-editing programs. "We do this by identifying the most effective gene modifications before investing in CRISPR or related genome-editing efforts, significantly improving efficiency and success rates."

Looking ahead, Shalitin emphasizes, "Our greatest hope is that systematic in-plant discovery and optimization will become an integral part of crop improvement, enabling faster development of resilient, high-yielding crops to address global agricultural challenges." He is further encouraged by the increasing acceptance of advanced gene-editing technologies, which he believes will help accelerate the widespread adoption of these approaches across agriculture.

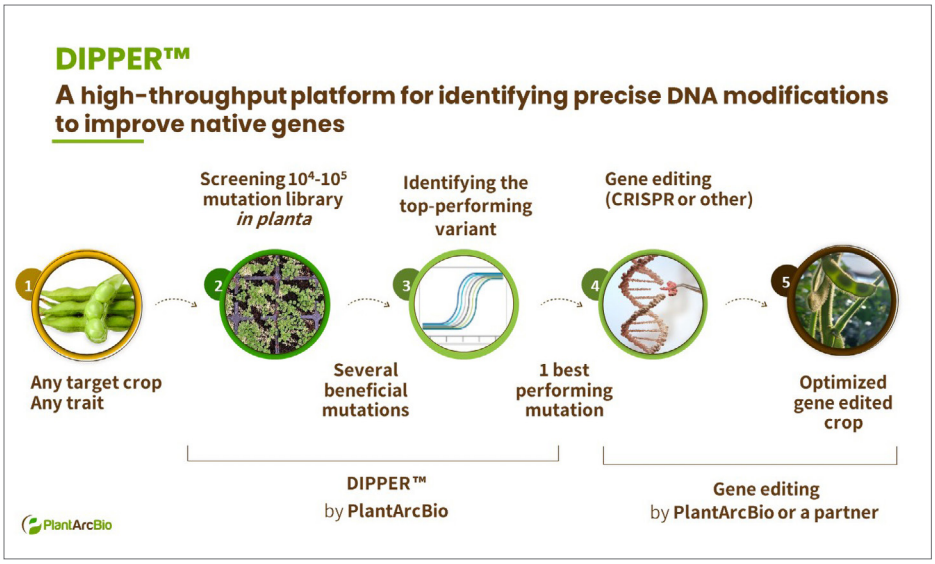


Illustration of crop trait improvement utilizing high-throughput screening of crop genes and CRISPR-mediated gene editing. [PlantArcBio]

Banana breakthrough

Ranking as one of the world's most widely consumed fruits, bananas also help sustain the livelihoods of millions of farmers worldwide. Yet they are particularly vulnerable to climate change issues since more than 90% of global exports rest almost entirely on a single cultivar, the Cavendish. Mihir Kekre, head of commercial partnerships at **Tropic Biosciences**, provides a perspective: "Bananas are a sterile crop and cannot be hybridized, leaving the industry unable to introduce new traits and favorable variation through traditional breeding to protect against global disease pressures such as Panama Disease and Black Sigatoka, which are threatening supply."

However, utilizing its GEiGS® platform and other gene editing technologies, the company recently made a breakthrough in engineering the first non-browning banana. Kekre comments, "In 2025, Tropic brought the world's favorite fruit into the 21st century with a new commercial variety, the first in over 75 years, with the launch of our non-browning Cavendish banana," Kekre comments. "The banana stays firm and yellow after peeling and slicing... has the same great flavor, texture, and aroma as the standard Cavendish banana we are accustomed to—but stays fresher for longer."

Kekre says the key innovation came from the company's ability to make very precise changes in the fruit's DNA that allowed them to switch off the gene responsible for polyphenol oxidase, an enzyme responsible for browning. "We create small, targeted edits to genes already present in the plant, without introducing any foreign DNA. Using this method, we are

able to 'fast forward' the natural breeding process, bringing about traits far more rapidly than conventional breeding. This approach is especially powerful for sterile crops such as banana and is considered non-GM with the emerging regulatory frameworks in most global geographies."

The impact and originality of Tropic's breakthrough were recognized by earning a place on *TIME* Magazine's Best Inventions of 2025. Kekre summarizes, "This innovation not only unlocks new opportunities across retail and food service categories but also significantly cuts waste throughout the supply chain."

In addition to collaborations licensing their GEiGS technology, Tropic is also working on other crops. Kekre notes, "In our rice program we have varieties resistant to Rice Blast, a fungal disease that destroys up to 30% of annual harvests, and 'increased yield' varieties which will enable more rice with less land, water, and emissions required—helping to improve food security, whilst reducing the pressure on natural resources."

Multiplex editing for breeding

One of plant breeding's biggest bottlenecks stems from the fact that many prioritized crop traits (e.g., durable disease resistance) are polygenic, requiring years of crossing to "stack" the correct alleles. Further, unwanted linked DNA may cross-contaminate the process, resulting in the need for repeated backcrossing. **Corteva Agriscience** is positioning multiplex genome editing as a way to break this bottleneck.

Jeffry Sander, PhD, program lead for genome editing, envisions CRISPR as a scalable breeding tool capable of editing multiple targets at once in order to accelerate trait creation and stacking. Thus, rather than editing one gene at a time, multiplex editing enables the simultaneous, targeted modification of multiple genomic sites within a single plant. This approach allows breeders to introduce, tune, or disable several trait-relevant genes in parallel to significantly compress timelines that once spanned years.

Sander also believes that integrating enabling technologies, including CRISPR-Cas, base editors, and other DNA-modifying tools, will not only improve multiplex efficiency, but also reduce development timelines for many types of crops. Technically, multiplex editing relies on the introduction of multiple guide RNAs (delivered together as plasmids, RNA/protein RNPs, or guide arrays) to direct genome-editing enzymes to different loci at once. Depending on the particular application, this approach can support gene knockouts, small sequence changes, or modulation of gene regulation.

Corteva has introduced its Genlytix™ ecosystem that is driving high-throughput editing, data analysis, and third-party collaborations that accelerate discovery initiatives.

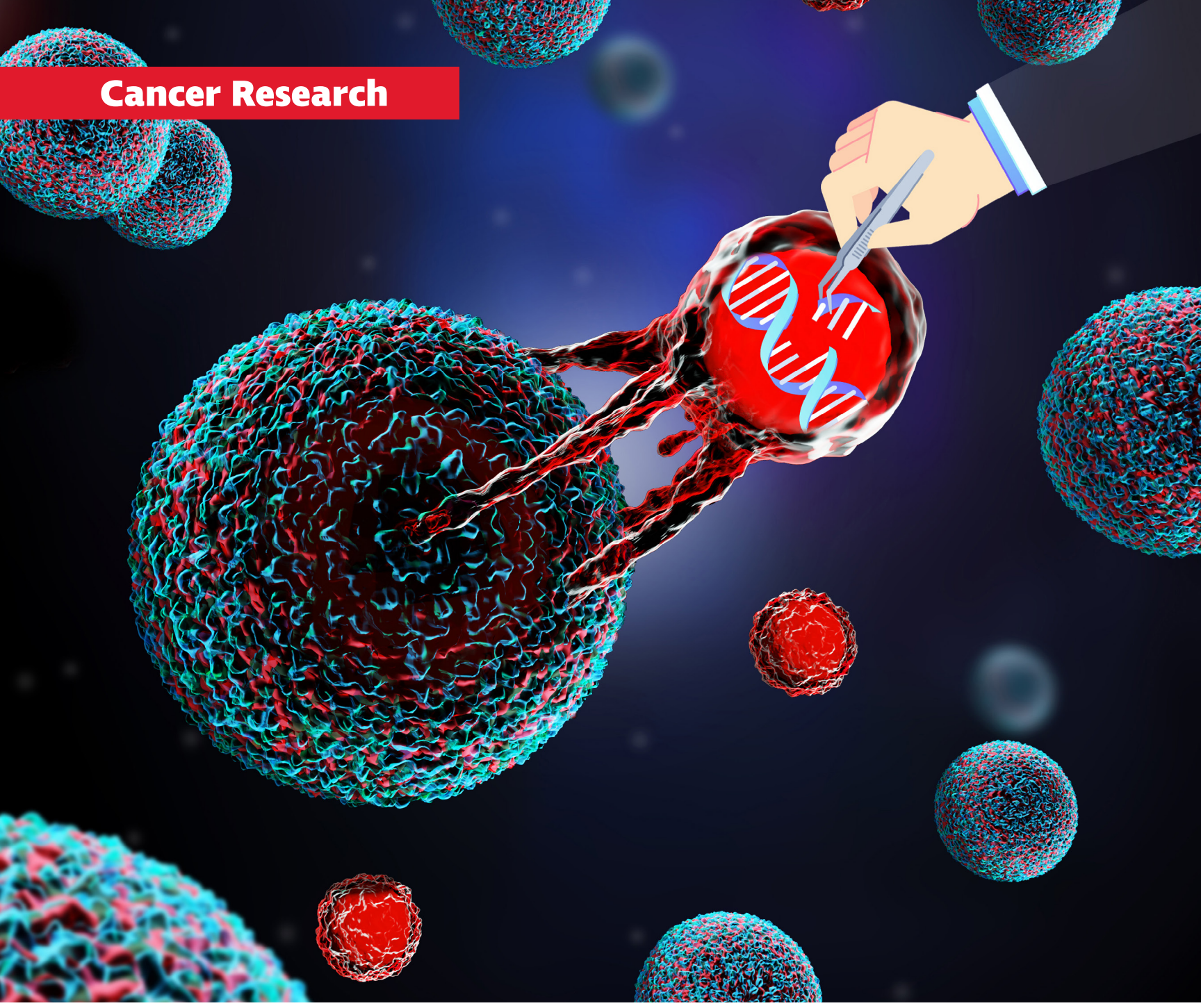
AI-driven trait discovery

In plant sciences, as with other fields, the ability to generate complex biological data often far exceeds the capability to translate those data into actionable targets. While genomics, transcriptomics, and large-scale phenotyping have become routine, identifying the critical genes and regulatory networks that control complex agronomic traits remains a slow and resource-intensive process.

Simplot Plant Sciences is employing a data-centric approach to plant trait discovery that integrates multi-omics datasets with agentic AI (i.e., systems that autonomously prioritize targets and adapt decisions as new data emerge). This strategy brings together genetic diversity panels, molecular profiling, and phenotypic measurements into unified machine-learning models designed to uncover non-obvious biological relationships.

By comparing AI-guided predictions with traditional statistical analyses, the platform may improve the reliability of target selection and reduce downstream validation failures. These insights can be directly coupled to CRISPR-based genome editing, enabling rapid functional testing and precise trait development. GEN

Scientists are employing precise gene editing and RNA-based trait control to develop rice varieties with improved disease resistance, resilience, and grain quality. [Tropic Biosciences]



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In Vivo CAR T Therapy

Will the Bets Pay Off?

By MaryAnn Labant

With clinical data beginning to emerge, big pharma is signaling its belief that *in vivo* CAR generation is the next immunotherapy breakthrough

The value of *ex vivo* autologous CAR T therapies is clear: for some patients, these treatments offer a second chance at life. Yet the approach comes with significant limitations. The patient-physician journey is complex, and manufacturing is both costly and logistically demanding, due to reliance on *ex vivo* manipulation of each patient's apheresis-derived T cells under GMP conditions.

The number of patients treated represents only a small fraction of those in need, limiting democratization of this groundbreaking treatment. Will *in vivo* CAR T therapies, positioned as off-the-shelf products, be able to break down these barriers and expand access?

A range of *in vivo* CAR T platforms—both integrated and non-integrated—are currently under investigation. Integrated approaches typically rely on viral vectors, such as lentivirus, similar to those used in most approved CAR T therapies. As with other viral gene therapy strategies, these platforms carry known risks, including the potential for insertional mutagenesis.

Despite these risks, early clinical data suggest meaningful potential for *in vivo* CAR T approaches. Two early studies—one performed by Belgium-based **EsoBiotec** in collaboration with China-based **Shenzhen Pregene Biopharma**, and another by Boston-based **Kelonia Therapeutics**—have demonstrated tumor clearance in multiple myeloma using lentiviral vectors.

Complementary non-integrated platforms use a variety of delivery methods, including lipid nanoparticles (LNPs), nanosomes, and exosomes. In these scenarios, the half-life of mRNA, the primary delivery vehicle, is a challenge, likely requiring the ability to redose without immunogenicity. DNA-based payloads are being investigated as alternatives.

Major pharmaceutical companies are racing to acquire *in vivo* cell engineering platforms, signaling that reprogramming cells inside the body is becoming a central pillar of therapeutic strategy. A wave of company consolidations demonstrates the impending expansion of this nascent, yet rapidly maturing, field beyond oncology applications to other disease arenas such as autoimmune disorders.

Specificity and scaling challenges

Early in 2021, **Sanofi** saw the potential and purchased **Tidal Therapeutics**. At the time, Sanofi anticipated that this next-generation, off-the-shelf approach had the potential to bring CAR T cell therapy to a much broader patient population.

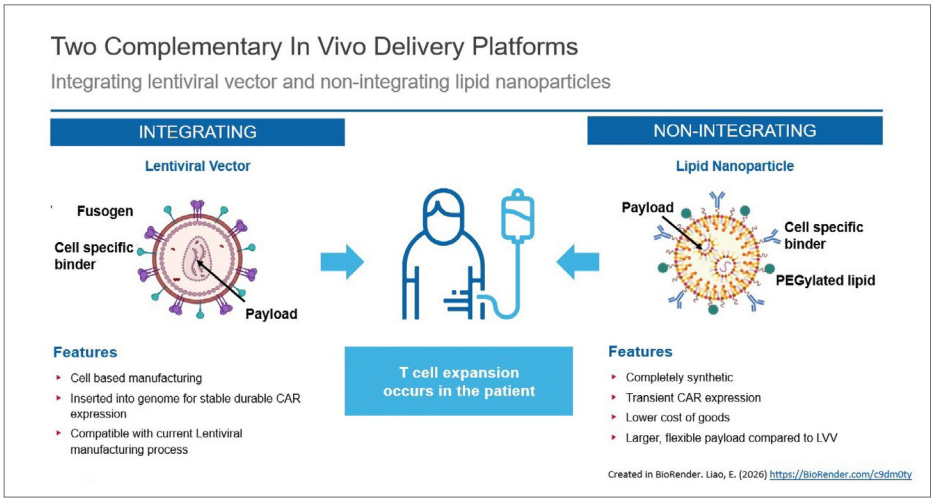
> **Despite risks, two early studies have demonstrated tumor clearance in multiple myeloma using lentiviral vectors.**

"To increase efficiency, we are working on non-integrated approaches that are targeted to deliver mRNA cargoes to specific cell types," said Christian Mueller, PhD, vice president and global head of genomic medicine at Sanofi. Sanofi's CD8-targeted LNP efficiently delivers CD19 CAR mRNA to CD8 T cells.

The ionizable lipid and its formulation enable efficient transfection of T cells *in vitro* and in animal models. In nonhuman primate (NHP) studies, administration of the targeted LNPs resulted in profound and sustained B cell depletion with few, and mostly transient, subclinical side effects.

"We engineer our targeting moieties to ensure that we have site-specific lipidation for incorporation into the LNP," explained Mueller. The site-specific location of the modification ensures batch-to-batch consistency and robust scalability relative to other LNP targeting methodologies.

Scaling can be challenging. Targeted LNPs require the manufacture of several different components, such as mRNA, lipids, and targeting moieties, all of which need to be formulated into a consistent drug product. Significant engineering development at Sanofi has enabled an efficient targeted LNP production process.



A range of *in vivo* integrated and non-integrated platforms are under investigation for *in vivo* CAR generation. Partnering lentiviral and lipid nanoparticle technologies can unlock next generation *in vivo* CAR therapies. [Kite, a Gilead Company]

Mueller predicts the durability of *in vivo* CAR expression will continue to improve. Multiple strategies exist, including the potential for LNP-mediated delivery of DNA to enable longer dosing windows, or even permanent expression of a CAR through gene insertion technologies. Continued development work over the next few years will reveal the appropriateness of these advanced payloads for varied applications.

CARs and CAR targets will continue to diversify beyond hematologic applications. Engineering may permit more complex circuitry that could unlock the full potential of an *in vivo* cell reprogramming approach, including, but not limited to, expression of factors to allow for the treatment of solid tumors.

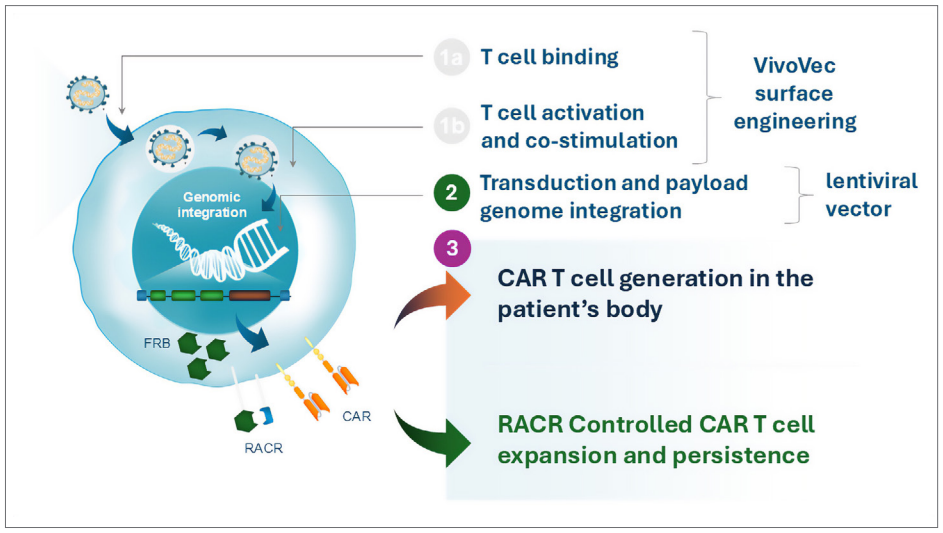
> **"*In vivo* CAR T cell approaches could bring us closer to the possibility of true cures."**
>
> —Jonathon Sedgwick, PhD, Senior Vice President, Global Head of Discovery Research, AbbVie

Sanofi is considering extended applications of their targeted LNP platform beyond *in vivo* CAR T to reprogramming of other cell types. In particular, the targeting of hematopoietic stem cells is interesting and could deliver potentially curative therapies to patients.

Acquisitions ramp up

More recently, industry dealmaking has accelerated. According to *Oncology Pipeline*, in 2025, **Bristol Myers Squibb** (**BMS**) acquired **Orbital Therapeutics** and its RNA-based *in vivo* pipeline for $1.5 billion. **Gilead**, through its subsidiary **Kite**, committed $120 million up front and up to $1.5 billion in milestone payments to partner with Chinese cell therapy specialist **Pregene**, before subsequently acquiring **Interius BioTherapeutics**.

Other large pharmaceutical companies have made similar moves. **AstraZeneca** acquired EsoBiotec for up to $1 billion, while AbbVie made headlines with its $2.1 billion acquisition of **Capstan Therapeutics** and a separate licensing agreement with **Umoja. Kelonia Therapeutics** has also announced a strategic collaboration with **Johnson & Johnson** to advance the discovery of novel *in vivo* CAR T-cell therapies.



The VivoVec platform combines lentiviral vector gene delivery with a T cell targeting and activation surface complex. VivoVec can be combined with RACR (rapamycin-activated cytokine receptor) to potentially enhance survival and expansion of VivoVec-engineered CAR T cells. [Umoja Biopharma]

Leveraging platform experience

The pace of technology and platform development in the 2020s far exceeds that of previous decades. AI-enabled access to information strengthens hypothesis generation while evidence-based knowledge accumulation from global trial networks accelerates clinical development.

"Although *in vivo* CAR generation is a nascent field, we have signals of great potential. The work done on *ex vivo* therapies, including Yescarta® and Tecartus®, that have been used to treat almost 23,000 patients to date, provides confidence in the approach with prior knowledge for comparison," said Priti Hegde, PhD, senior vice president and global head of research, Kite, a Gilead Company. "The level of investment is significant. The applications are vast. If we can get these platforms to work, it will be game changing."

An outstanding question is whether a CAR alone has the ability to do its job, expand, and kill target cells in the absence of a lymphodepletion regimen to eliminate immunosuppressant cells. "Clinical data and long-term patient monitoring are needed to understand if *in vivo* approaches are as durable and provide similar clinical characteristics as *ex vivo* platforms," emphasized Hegde.

Due to experience with lentiviral *ex vivo* platforms, Kite elected to use a lentivirus-based platform for *in vivo* CAR development work. To prevent non-specific delivery, the engineered virus is coated with a targeting moiety to specifically deliver the payload to a cell expressing the target. Changing the targeting binder and the payload provides diversity for application to different cell types and diseases, as well as for crucial IP creation.

Hegde pointed out the critical impor-

tance of manufacturing at scale. "We have invested a lot of effort into manufacturing lentivirus. The acquisition of Interius BioTherapeutics complements our internal development work."

Interius's scalable modular model for viral vectors allows faster program development. The first program in dose escalation Phase I studies in Australia and Europe is targeted towards CD20 in lymphomas and uses a non-activating binder that targets CD7 on T cells. "Now that the manufacturing program is integrated into Kite Research, we are exploring other binders and CAR constructs," Hegde added.

Taking both approaches

AbbVie is currently investigating *in vivo* CAR T platforms across immune-mediated diseases and cancer.

"*In vivo* CAR T cell approaches could transform how we address difficult-to-treat autoimmune diseases and cancers, potentially bringing us closer to the possibility of true cures," said Jonathon Sedgwick, PhD, senior vice president and global head of discovery research at AbbVie. "The approach could overcome major hurdles of autologous CAR T therapies and may eventually help expand the patient population benefiting from CAR T therapies."

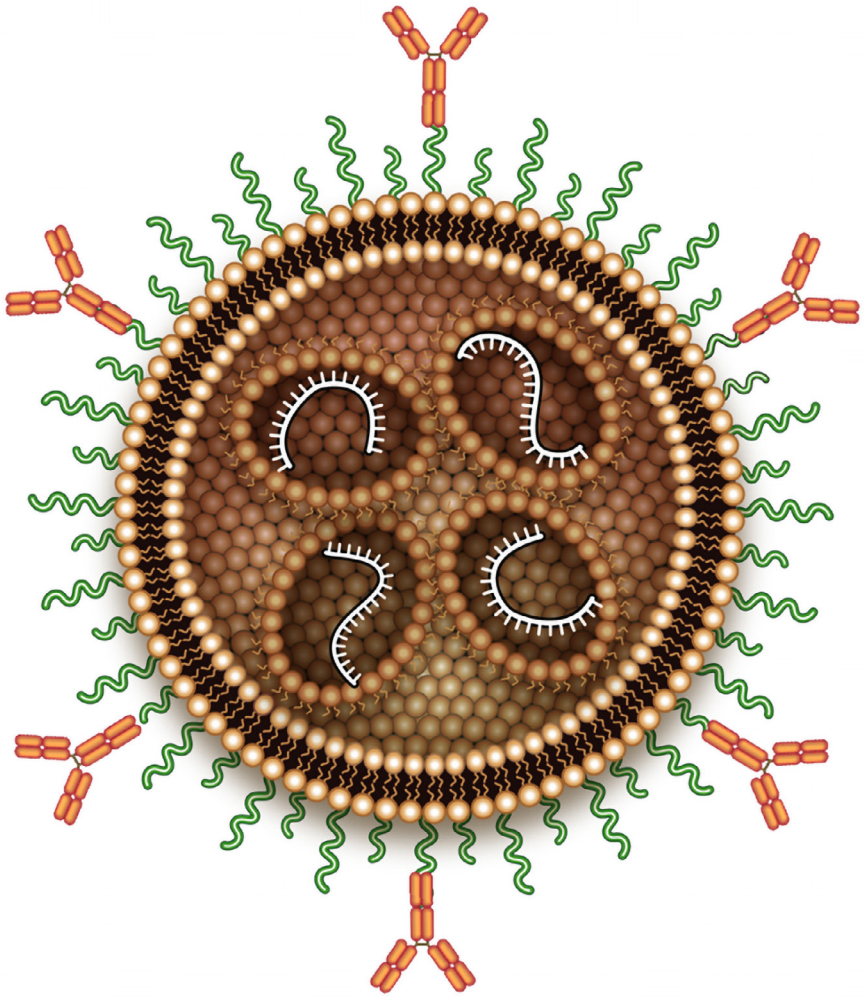
One method uses a proprietary targeted LNP (tLNP) platform for RNA delivery, initially developed by Capstan Therapeutics. The tLNPs are designed to minimize off-target effects, including liver de-targeting chemistry. Targeting binders on the LNPs that recognize specific T cell surface markers enables delivery of RNA to desired T cell populations, transiently converting them into CAR-expressing cells that can seek and destroy pathogenic cells known to drive certain autoimmune diseases.

According to Sedgwick, ABBV-619 is designed to program CD8+ T cells in the patient's body to express CD19-specific CARs. By generating these CD19 CAR-expressing cytotoxic CD8 T cells, the approach aims to deplete pathogenic memory B cells in the periphery and tissues that, in turn, enables repopulation with naïve B cells, potentially resetting the immune system to halt or reverse disease progression. ABBV-619 is currently in Phase I studies for the treatment of B cell-mediated autoimmune diseases.

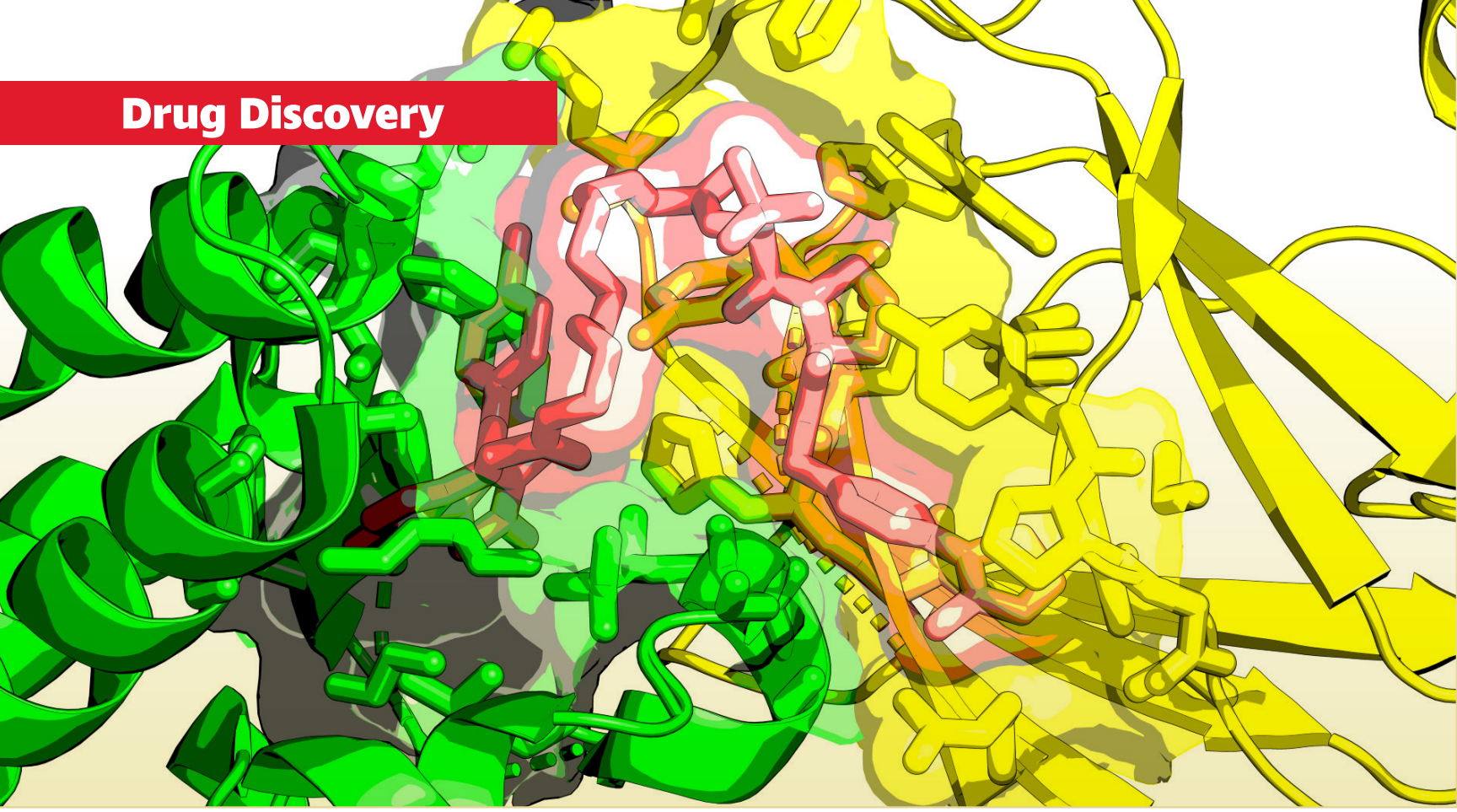
The company's partnership with Umoja leverages the proprietary VivoVec™ platform to develop *in vivo* CAR T therapies for oncology. The platform combines third-generation lentiviral vector gene delivery with a novel T cell targeting and activation surface complex. VivoVec can be combined with RACR (rapamycin-activated cytokine receptor) to potentially enhance survival and expansion of VivoVec-engineered immune cells.

AbbVie holds an exclusive option to license Umoja's CD19-directed *in vivo* CAR T candidates, including UB-VV111, Umoja's lead clinical program for hematological malignancies currently in Phase I studies.

"By drawing upon our deep heritage in immunology and oncology, leveraging our internal capabilities, along with strategic investments and partnerships, we are committed to advancing *in vivo* CAR T platforms to create more accessible, durable, and transformative therapies to target a broad range of pathogenic cell types," said Sedgwick. GEN



A schematic representation of a targeted lipid nanoparticle (tLNP) carrying an mRNA payload, with targeting binders on the exterior to direct it to the desired T cell populations. [AbbVie]



Expanding the Druggable Proteome with Tech Advances

How PROTACs, molecular glues, and macrocycles are reshaping drug discovery in 2026

By Tiffany Yesavage, PhD

Drug discovery has long faced a stubborn reality: Most disease-relevant proteins lack the deep, hydrophobic pockets required for inhibition by conventional small-molecule drugs. Beginning in the early 2000s, researchers began framing this challenge in terms of *druggability*—whether a given protein can bind effectively to traditional therapeutics.[1] Transcriptional regulators, scaffolding proteins, and intrinsically disordered domains were therefore often considered largely *undruggable*.

Over the past decade, however, a wave of technological advances has begun to expand the druggable proteome. These include covalent inhibitors (such as sotorasib), chemical proteomics, and AI-enabled structural prediction tools like AlphaFold. We spoke with four leading experts to explore two additional therapeutic modalities gaining momentum in 2026: targeted protein degraders and macrocycles.

Targeted protein degradation

Targeted protein degradation (TPD) is a therapeutic strategy that aims to destroy disease-causing proteins within cells. "Traditional therapies with small-molecule drugs tend to focus on inhibiting problematic proteins. In contrast, TPD aims to completely eliminate these proteins," explains Alessio Ciulli, PhD, professor at the University of Dundee and founder of the Centre for Targeted Protein Degradation.

Above. The structure of the MZ1 PROTAC (*red*), which includes a linker and two ligands that simultaneously bind to the BRD4 target protein (*green*) and an E3 ligase called VHL (*yellow*).[4,5] [Created by A. Ciulli]

More specifically, degrader drugs bring the disease-causing target protein into proximity with an E3 ligase—an enzyme that is part of the cell's protein degradation machinery.

"TPD works in a clever way by hijacking the cell's own trash disposal mechanisms," Ciulli says. "We are borrowing from nature and saying, 'Come and help me get rid of these proteins.'"

"A major advantage of TPDs is that, unlike traditional small-molecule drugs, they bind only transiently with their intended targets and do not require a well-defined binding pocket," notes Gwenn Hansen, PhD, CSO of **Nurix Therapeutics**. "This enables the elimination of previously undruggable proteins."

PROTACs versus molecular glues

The TPD field consists of two major classes of degraders—PROTACs (PROteolysis TArgeting Chimeras) and molecular glue degraders. PROTACs are small molecules that consist of three key parts: 1) a ligand that binds the disease-causing protein, 2) a ligand that binds an E3 ligase, and 3) a chemical linker connecting the two.

"PROTACs are like matchmakers," notes Ciulli. "They follow a plug-and-play strategy in the sense that you can mix and match any target protein with any E3 ligase. It is like two hooks and a way to connect the hooks."

"It is almost like your PROTACs build bridges on demand," he continues. "You say, 'Hey, I want to get from protein A to protein B. Let's build the bridge that allows us to do that.' Because you know exactly what A and B are."

Although dozens of PROTACs are advancing through clinical trials as of early 2026, none of them have yet received full FDA approval.

Molecular glues are another type of TPD. Instead of generating entirely new protein–protein interactions, as with PROTACs, molecular glues require a pre-existing surface complementarity between the two proteins. More specifically, they enhance the binding of the target protein to the E3 ligase, in a mechanism called *gluing*. Thalidomide, lenalidomide, and pomalidomide are clinically approved molecular glue degraders.

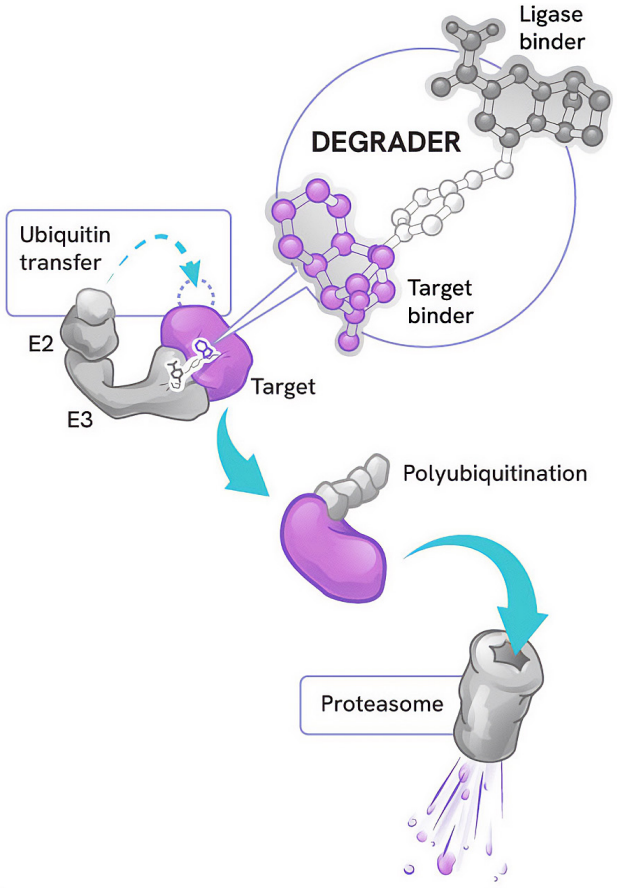
Ciulli relates how the precise molecular mechanism of thalidomide wasn't established until the 21st century, when researchers identified its target, the E3 ligase cereblon. Tragically, the drug led to thousands of congenital abnormalities in children whose mothers had taken it during early pregnancy in the 1950s and 1960s.

Like PROTACs, molecular glues are small molecules (they lack a linker and only feature one of the two binders). "Compared with PROTACs, glues are much more minimalistic," notes Ciulli. "They don't have this plug-and-play of PROTACs. The proteins already have some intimacy, but it is not quite there. And then, BOOM, molecular glues make it happen."

Which is more promising for the future, PROTACs or molecular glues? "They are both important. They are absolutely both the future," argues Ciulli. "They both need to be deployed conceptually and practically if we really want to drug some of these cancers."

"To some extent, PROTACs and molecular glues are really a continuum," adds Ciulli. "It is not like we are talking about apples and pears. It is more like oranges and mandarins. The mechanism is exactly the same. We are degrading the protein in the end."

Hansen notes that Nurix is primarily focused on PROTACs, which she describes as "the most tractable modality for targeted protein degradation." However, the company is also developing



PROTACs (*upper right*) enable E3 ligases (*gray*) to tag unwanted proteins (*pink*) with ubiquitin molecules, marking them for destruction by the proteasome (*bottom*), the cell's recycling center. [Nurix Therapeutics]

molecular glues as well as a newer TPD modality called degrader antibody conjugates (DACs), which couple PROTACs to antibodies.

TPD for new targets

"Nurix is currently emphasizing previously undruggable targets that sit at the heart of disease biology—including a lot of signaling proteins and transcriptional regulators," notes Hansen.

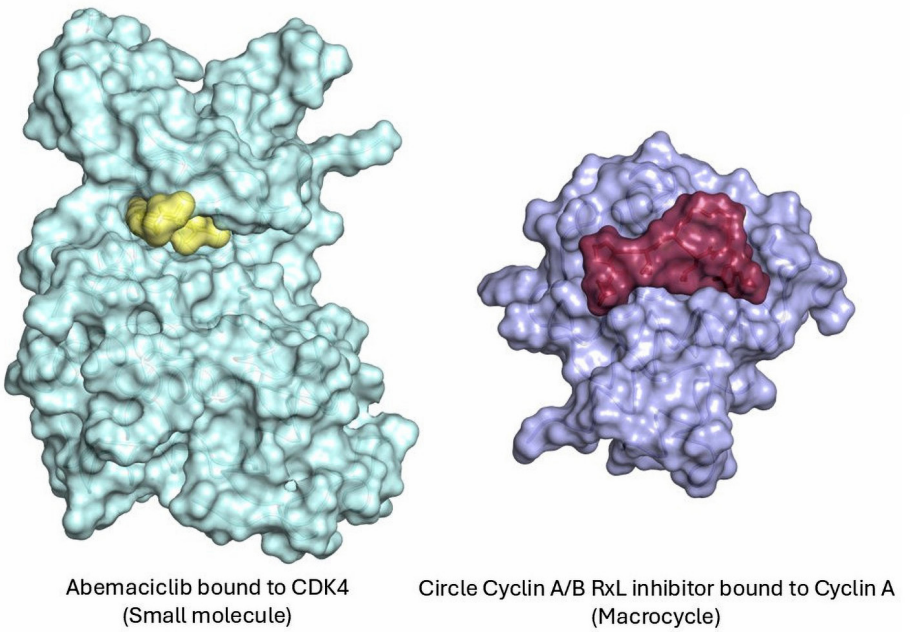
Nurix's high-throughput approach leverages a combination of proprietary DNA-encoded libraries, synthetic chemistry, and machine learning to rapidly identify and optimize their TPDs. The company's current pipeline consists of several oncology and immunology targets.

Likewise, Ciulli stresses that his lab is "working on really tough targets that we previously wouldn't dare to touch." More specifically, he is focused on cancers driven by specific genetic alterations, such as mutations, translocations, and genetic fusions. "These events generate proteins that are very, very hard to target," he says. Such proteins tend to have multiple structures that are hard to predict with technologies like AlphaFold. In other cases, these proteins are recycled very, very quickly.

Ciulli notes the success of PROTACs in targeting KRAS,[2] which is often highly mutated in cancer. Small-molecule drugs typically target only very specific KRAS mutations that affect around three percent of patients.

"In contrast, we published a PROTAC degrader that we were able to show removes 13 out of 17 of all of the known oncogenic drivers of cancer. With PROTACs, a single molecule can degrade all of the KRAS mutations."

Finally, Hansen highlights the ability of TPDs to degrade disease proteins that have developed mutations or acquired resistance following treatment. "By eliminating a protein entirely rather than transiently inhibiting its function, degraders can achieve deeper and more durable control or even elimination of disease," she notes.



Abemaciclib bound to CDK4 (Small molecule)

Circle Cyclin A/B RxL inhibitor bound to Cyclin A (Macrocycle)

Circle's lead program (an oral macrocycle that inhibits cyclin A/B RxL) is currently in late Phase I clinical development. For size comparison, the small molecule drug abemaciclib is shown at the same scale (*left*). [Circle Pharma]

"Looking forward, I expect the field to move away from proving that degradation works and toward proving *where it wins*," she predicts. "The companies that win will be the ones that treat degradation as a drug-discovery discipline, not an alternate and occasional modality."

Introducing macrocycles

David J. Earp, PhD, president and CEO of **Circle Pharma**, explains how the company is developing a class of compounds called macrocycles to treat cancer. "Macrocycles offer the potential to drug targets that have eluded other drug modalities," he notes.

Macrocycles are large, ring-shaped molecules that provide structural support and allow for effective binding to biological targets. Cyclosporine and erythromycin are two examples of macrocycle drugs derived from nature. Over the past decade, there has also been a strong interest in developing fully synthetic macrocycles, and these efforts have generated early clinical success.

"Peptidic macrocycles occupy a compelling middle ground between biologics and conventional small molecules," he notes. Unlike biologics, macrocycles are small enough to enter cells and can be orally available when properly engineered. On the other hand, macrocycles are larger than small-molecule drugs. In larger targets, this allows for multiple contacts across a broader area.

Like Circle, **Curve Therapeutics** is also developing macrocycle peptides. Ali Tavassoli, PhD, CSO of Curve and professor of chemical biology at the University of Southampton, explains that the company is focused on small cyclic peptides—called microcycles—composed of only six amino acids in a head-to-tail ring. They are generated in mammalian cells during a post-translational process called intein (internal protein segment) splicing.

Unlike larger cyclic peptides from other technologies, the key binding regions of microcycles (pharmacophores) work through just three or four amino acids. "Therefore, they are ideally positioned for further peptide engineering and modification with non-peptide components. They also have the potential for scaffold hopping into small molecules," says Tavassoli.

Curve is currently producing and screening libraries of around a billion microcycles directly inside mammalian cells, selecting hits based on function inside a disease-relevant environment. Curve's function-based approach is unique, as other companies emphasize binding as the primary readout.

"Binding in a test tube doesn't guarantee function in a cell," emphasizes Tavassoli. "We screen for biological function inside live mammalian cells, where targets exist in native conformations with disease-relevant modifications. They ask, 'What binds?' while we ask, 'What functions?'" Curve's intracellular screening process involves genetically encoded cyclic peptide libraries and fluorescence detection.

Success with macrocycles

Curve's lead program is a first-in-class dual HIF-1 and HIF-2 inhibitor that disrupts proteins that enable cancer to thrive in low-oxygen tumor environments. The company is also pursuing FOXA1 inhibitors for hormone-refractory breast cancer, for which no inhibitors exist despite significant R&D interest in the target.

Meanwhile, Earp highlights two programs in Circle's macrocycle pipeline that directly target cyclins, master regulators of cell division that are frequently dysregulated in cancer. "Historically, cyclins were considered undruggable, as prior efforts using traditional small molecules failed to effectively target these highly dynamic intracellular protein–protein interfaces."

Circle's lead program, CID-078 (an oral macrocycle cyclin A/B RxL inhibitor), is currently in late Phase I clinical development for solid tumors.[3] "We are progressing very efficiently through dose escalation and have excellent clinician engagement," notes Anne E. Borgman, MD, chief medical officer. Clinical data will be available in 2026.

The company also anticipates filing an IND for a second program (CID-165, a cyclin D1 RxL inhibitor) with potential applications in ER-positive breast cancer and lymphomas. Both programs represent first-and-only-in-class approaches, says Earp.

Beyond cyclins, Circle hopes to apply its macrocycle platform to other high-value oncology targets that remain inaccessible to conventional small-molecule drugs—including transcriptional regulators and scaffolding proteins. The company aims to access intracellular targets and achieve oral bioavailability.

Tavassoli and Earp agree that intracellular delivery remains a major hurdle for cyclic peptides. Fortunately, AI-driven design, new cyclization chemistries, and non-natural amino acids are transforming what is possible, notes Tavassoli. He predicts that multiple drugs from cyclic peptide platforms will be approved within the next decade to target proteins.

"As these tools mature, we expect macrocycles to play an increasingly central role in expanding the druggable proteome, particularly in oncology and other areas driven by challenging intracellular protein–protein interactions," adds Earp. GEN

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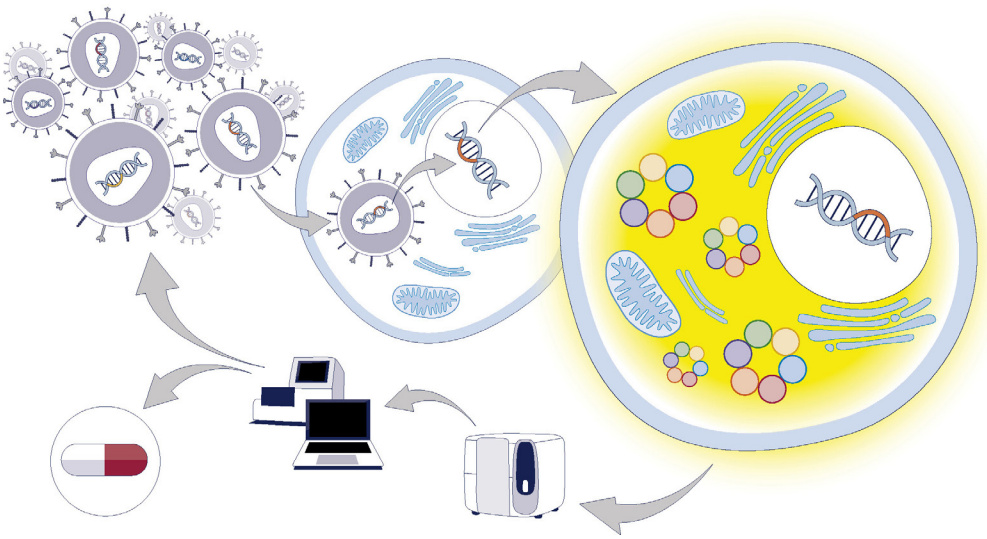


Curve Pharma's Microcycle-encoding genes are packaged into lentiviral vectors (upper left) and transduced into a screening cell line. Microcycles that modulate target activity are detected through fluorescence methods.

Standouts among Non-CHO Cell Expression Systems

Sproetniek/ E+ / Getty Images

Non-CHO cell expression systems gain traction as faster, more flexible alternatives for biologics manufacturing

By Gail Dutton

Chinese hamster ovary (CHO) cell lines are one of the most-used cell-based protein expression systems for therapeutics, thanks to their ability to support post-translational modifications such as glycosylation. That makes them valuable for producing antibody-drug conjugates (ADCs), monoclonal antibodies (mAbs), and therapeutic vaccines.

Despite CHO cells' expanding applications, other protein expression systems may be at least as valuable in terms of rate of replication and ease of manufacturing. Cell-free expression systems are gaining traction, and use of the widely used *Escherichia coli* (*E. coli*) remains strong. Manufacturers also are assessing possibilities in avian-, plant-, fungal-, and insect-based cell cultures.

Cell-free systems

"The idea of expressing protein in bacterial extract goes back to the founding of **Genentech** in 1975, where the first products were produced in bacteria," Hans-Peter Gerber, PhD, CSO of

Sutro Biopharma, says. "Simple peptide growth factors were small and easy to manufacture, but when they moved to antibody therapeutics, which are larger molecules, they realized a quick bacterial approach wouldn't work." The solution was to engineer cell expression systems and to look at alternative systems.

Sutro Biopharma is among those companies that engineered bacterial extracts into a cell-free expression system.

"We use the cell-free system to make oncology medicines, specifically oncology ADCs, for targeted chemotherapy," Jane Chung, CEO of Sutro Biopharma, tells *GEN*.

"The design of an ADC is very complex because it requires engineering not only an antibody, but a linker and a payload," Chung points out. These components must be considered both individually and as a part of the whole. "A cell-free system gives far greater flexibility and control of the design, including where the linker payloads are attached to the antibodies."

Such precise configuration enhances consistency of the medicine that's delivered to patients, Chung says. Specifically, "When we configure a drug to antibody ratio (DAR) as a DAR 8, it's a DAR 8—not an average," thus ensuring patients receive precise, consistent dosages.

Additionally, Gerber says, "When we produce proteins with cell-free extracts, we can make more proteins faster, test them quicker and learn faster—especially with AI and machine learning—and, recently, make them as cheap or cheaper even than [with] CHO cells."

Producing ADCs in a cell-free system is relatively easy, he continues. "We can generate 10,000 unique ADC molecules because all we have to do is make different DNAs and code for the different ADCs. We put unique DNA sequences into 10,000 tubes of extract, and they're conjugated overnight and tested for activity within two weeks. The best you can do with CHO cells—and I've done that for 25 years—is to generate 10 to 100 ADC molecules within three to six months, and then select the lead candidate from among them."

"High throughput screening is a key differentiator for us on the cell-free platform," Chung observes, helping Sutro identify the optimal lead candidate from a wider field and thus de-risk development.

Reaching this point involved certain challenges, of course, that can be addressed with engineering. For example, "Bacteria don't naturally form cysteine bridges between two protein chains, so we had to engineer them," Gerber elaborates. The resulting proteins also needed to meet the same or higher quality than those of CHO cells. The U.S. Food & Drug Administration (FDA), he says, reached out to Sutro to collaborate on generating standard ADCs with precise DARs that serve as reference compounds for ADCs derived from CHO cells.

> **"Plant-based systems are an alternative way to produce complex proteins in a way that addresses some of the limitations inherent to mammalian-based expression systems."**
>
> —Ori Kalid, PhD
> Vice President, R&D, Protalix

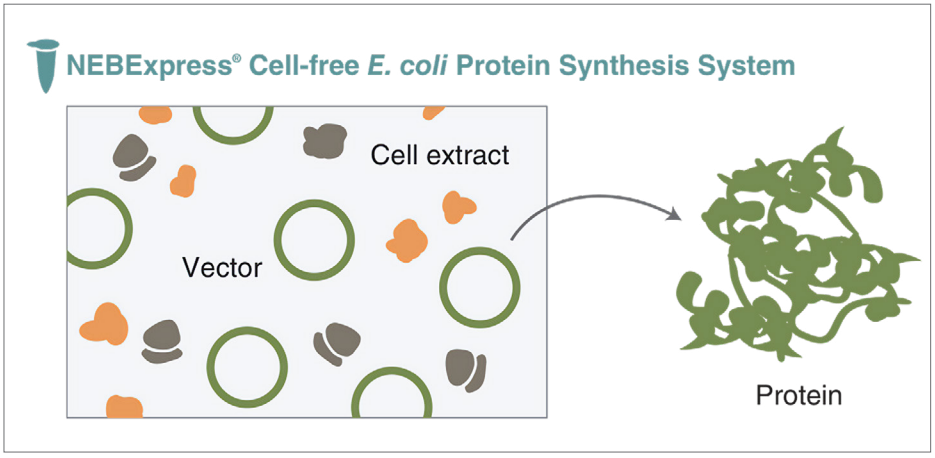
Post-translational modifications—like glycosylation—of proteins and antibodies also can be challenges in cell-free systems. But, Gerber points out, preventing glycosylation can be a "huge advantage" because glycan-induced toxicities are avoided.

Industry-wide, Gerber predicts more companies will move into cell-free mammalian systems.

E. coli systems

E. coli is the go-to organism for large-scale production of enzymes at **New England Biolabs**, according to Brad Landgraf, PhD, process development group leader, formulation and purification discovery. While CHO cells are often the system of choice for complex mammalian proteins, *E. coli* is a go-to system for a plethora of other proteins.

"*E. coli* is the first organism you would try and has been our workhorse organism for making recombinant proteins," Landgraf says. "It's simple, fast, and easy. The genetic system is very well understood, and we know how to manipulate it very



E. coli is the organism of choice for large-scale enzyme production at New England Biolabs because the organism is well-understood and applications are fast and easy. [New England Biolabs]

well. It's relatively cost-effective and it grows quickly, doubling every 15 minutes at 37°C." The platform produces enzymes required for vaccine manufacturing, rather than the vaccines themselves.

The main limitation of *E. coli* is its inability to install complex post-translational modifications, such as glycosylation. *Kluyveromyces lactis* (*K. lactis*) or *Pichia pastoris* (*P. pastoris*) are alternative systems in those instances, he says, "even though they're very simple yeasts."

Avian systems

GeoVax is transitioning from primarily avian cells to a continuous avian suspension system, AGE.1. "That places us squarely within the broader industry shift toward more scalable and resilient non-CHO manufacturing platforms," David Dodd, CEO, tells *GEN*.

By transitioning modified vaccinia Ankara (MVA) vaccine production from primary chicken embryo fibroblasts (CEF) cells to the AGE.1 cell system, GeoVax expects to "improve consistency, scalability, yield, production speed, and long-term supply reliability," Dodd says.

Before making the transition, the company evaluated four avian cell lines that had already been reviewed by regulators. AGE.1, which the company ultimately selected, showed "a tenfold increase in productivity and held that advantage across [about] 15 passages, and it was more than five times better than the other avian cell lines."

Developing MVA vaccines in the AGE.1 cell expression system provides the surge capacity needed for both pandemic and niche applications, while enabling the vaccines to engage multiple targets and elicit both antibody and T cell responses, he says. GeoVax is using this approach with its SARS-CoV-2 vaccine, targeting the original strain through Omicron strains in a single vaccine. "We're getting eight to 12 months of protective immunity, versus three to six for mRNA," Dodd says.

Plant-based systems

Protalix is, to date, the only company to have received approval from the FDA and other regulators to manufacture and market plant cell-derived protein therapeutics. Two drugs have been developed in-house, approved, and out-licensed, and a third is in Phase II trials, says Dror Bashan, CEO.

The company is developing and manufacturing protein therapeutics using ProCellEx®, a proprietary plant cell-based expression platform. In it, plant cells are cultivated in suspension using disposable bioreactors that enable efficient, scalable, and cost-effective production of recombinant therapeutic proteins.

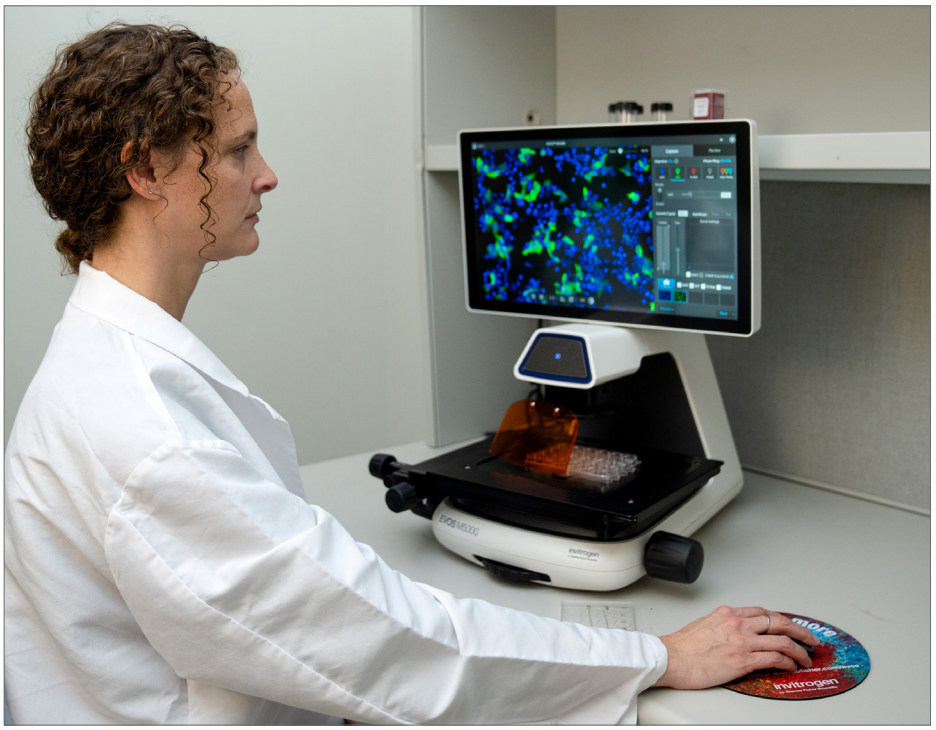
Plant-based systems "are an alternative way to produce complex proteins in a way that addresses some of the limitations inherent to mammalian-based expression systems," Ori Kalid, PhD, vice president of R&D, says.

Advantages include competitive costs, robust production that survives fluctuations in growth conditions, a high safety factor due to the lack of mammalian pathogens in plants, and the ability to produce difficult-to-express proteins.

"Producing proteins in plant cells is very simple compared to CHO because of simpler culture conditions and media," Uri Hanania, PhD, senior director of plant cells and genomic development, says.

Initially, Protalix used only very simple, well-known vectors to express proteins, but found that they yielded very low levels of recombinant proteins. Since those early days, the company's scientific team has developed advanced systems that integrate highly effective viral vectors into proprietary, genetically engineered platforms compatible with *Nicotiana benthamiana* cell lines. "Expression levels are about 100 times greater than the initial system," Hanania says, "reaching grams per kilogram cell scale, depending on the protein to be produced."

ProCellEx "provides mammalian-like post-translational modification patterns," Kalid adds, "and enables controlled pro-



GeoVax scientists migrate vaccine production from primary avian cells to a continuous avian suspension system, AGE.1, to enhance scalability and response resilience. [GeoVax]

duction of key glycosylation patterns that are critical for protein activity and biodistribution." Additionally, it provides "a robustness that enables the expression of proteins that may be toxic to mammalian systems, such as specific enzymes, cytokines, hormones, and other proteins." Notably, "The glycan profile produced by the plant system… [enabled by genetically-modified host cell lines] is less complex than that produced in mammalian cells, thus providing a regulatory advantage," Kalid adds.

"The expression level for this plant-based system varies among protein targets, and the ability to produce antibodies appears to be limited. However, because Protalix manufactures highly potent enzyme therapies for rare diseases, which require modest production volumes, this constraint has limited practical impact," Kalid says. It is readily scalable and is being continuously improved, he adds.

Fungal systems

Dyadic's fungal cell expression platform, C1, is a proprietary *Thermothelomyces heterothallica*-based system for producing mammalian-like glycoproteins used in mAb development. It enables faster, lower-cost production of complex proteins for mAbs, vaccines, and reagents than CHO cells, while operating across a broader range of temperatures and pH levels, says Mark Emalfarb, founder and CEO.

Using its C1 expression system, the company has completed Phase I trials in Africa for a COVID vaccine. That trial shows "we're hitting the proof points in terms of yields and analytics," Emalfarb says.

The C1 system is attracting interest from international organizations as a potential way to quickly scale up production for pandemic responses and for regional outbreaks. It has a doubling time of about two hours, compared with more than 20 hours for either CHO cells or baculovirus. Emalfarb adds, "Our manufacturing process is seven days in the fermenter, compared to 12 to 14 days for other processes." In a pandemic scenario—for avian flu, for example—he says the C1 expression system could produce 300 million vaccine doses within two weeks using one 15,000-liter bioreactor.

In terms of mAbs, the C1 platform can move from DNA to purified material in about eight weeks, compared with more than 20 weeks for CHO production systems, Emalfarb says. The difference is that C1 cells can enter production and purification immediately after the product strain is selected, whereas CHO systems require clone isolation and screening, followed by creation of a working cell bank and seed train before production can begin.

Dyadic is partnering with the Gates Foundation, CEPI, and the Fondazione Biotecnopolo di Siena to increase the speed of vaccine development, and with other organizations, including the National Institutes of Health, on other vaccine or mAb projects.

Future

Novel organisms will continue to emerge as cell expression systems, but the main workhorses—including *E. coli*, CHO cells, *P. pastoris*, and *K. lactis*—are likely to remain so for some time.

Taken together, these approaches suggest that while CHO cells will remain foundational, alternative expression systems are increasingly reshaping how biologics are developed and manufactured. Landgraf says, "I really think the future of protein production is in cell-free [production]. The reason is that it's very simple. You basically add DNA to your reaction and it makes the protein within hours, and you often can go directly from the protein synthesis reaction straight into an activity or functional assay to characterize that protein without extensive purification." GEN

Protalix's ProCellEx®, a proprietary plant cell-based expression platform, cultivates plant cells in suspension using disposable bioreactors for efficient, scalable, and cost-effective production of recombinant therapeutic proteins.

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Birgit Girshick

EVP & COO, Charles River

Birgit Girshick, will take over as CEO of the company in May 2026 upon the retirement of Jim Foster.

With more than 35 years at Charles River, Girshick is widely recognized for her strategic vision and deep commitment to scientific and operational excellence. In her new role, she will build on the company's strong foundation by accelerating innovation and sustainable growth.

James Foster

President & CEO
Chair of the Board, Charles River

Jim Foster will leave after a 50-year career at Charles River where his previous positions included vice president of administration and general counsel, president of Charles River Biotechnical Services, and executive vice president.

Tony Wu, PhD, has been appointed to **INTEGRATED BIOSCIENCES'** scientific advisory board.

START has elected **Frank Smith, PhD**, as president of its **XENOSTART** preclinical research business unit.

Elena Helman, PhD, has been named vice president of oncology solutions at **ULTIMA GENOMICS**.

CELCUITY has appointed **Charles Romp** to its board of directors.

HELUS PHARMA has welcomed **Michael Cola** as chief executive officer.

IORGANBIO has named **Karol Jarzabek** as chief operating officer.

VARIANT BIO has announced **Craig T. Basson, MD, PhD**, as chief medical officer.

SINGLE USE SUPPORT has announced **Davy De Wilde** as chief commercial officer.

ORYZON has hired **Rolando Gutierrez-Esteinou, MD**, as chief medical officer.

Francis Wilson, DPhil, has joined **AVACTA** as chief scientific officer.

ADARX PHARMACEUTICALS has appointed **Donald Fong, MD**, as chief medical officer.

N4 PHARMA has appointed **David H. Solomon, PhD**, as chief executive officer.

Walter Koroshetz, MD, has joined the **DANA FOUNDATION** as senior advisor.

Nawal Ouzren has stepped down as CEO of **SENSORION**, and **Amit Munshi** has assumed the role of interim CEO.

COMPANY INDEX

ADVERTISER INDEX

Products To Watch

Magnetic Workflow for Cell-Free DNA Extraction

New England Biolabs has released the Monarch® Mag Cell-free DNA (cfDNA) Extraction Kit, a bead-based method designed for scalable and reproducible isolation of low abundance cfDNA from plasma, serum, urine, and cerebrospinal fluid. The method supports input volumes from 1 to 4 mL and recovers short DNA fragments using silica-coated magnetic beads and specialized chemistry suited to nuclease-rich biofluids. The kit is compatible with manual or automated processing and aligns with the broader Monarch portfolio through reduced plastic usage and integration with NEB's downstream sequencing and amplification solutions.

New England Biolabs
www.neb.com

Single-Cell Partitioning System

RAN Biotechnologies has introduced the OrchestRANum™ System, a compact platform designed for single cell analysis. The system integrates optimized hardware, consumables, and flexible protocols to support customizable partitioning of cells into barcode droplets for molecular biology workflows. With scalable kits accommodating inputs from 5,000 to 80,000 cells, the platform is intended to broaden access to single-cell RNA sequencing and related applications across a range of research environments.

RAN Biotechnologies
www.ranbiotechnologies.com

Automated Vial Inspection Platform

Syntegon has introduced the AIM9, a high-throughput inspection platform designed to support pharmaceutical manufacturers and CMOs with combined visual inspection and leak detection capabilities. The system processes up to 600 vials per minute and accommodates vial sizes ranging from 2 to 250 milliliters. Its integrated Container Closure Integrity Testing options include headspace gas analysis and high voltage leak detection. With flexible changeover features and support for advanced inspection tools such as deep learning and bubble masking, the platform is engineered to deliver consistent detection performance and low false reject rates in production environments.

Syntegon
www.syntegon.com

High-Throughput Mass Spec Integration

SCIEX has expanded the capabilities of the Echo® MS+ system through new compatibility with the ZenoTOF 8600 system, creating a high-throughput accurate mass platform. The integration enables direct, label-free measurement across a broad range of compounds and supports assays that are difficult to achieve with conventional mass spectrometry. Key features include contactless sample ejection using as little as 2.5 nL, minimized sample preparation, and sampling rates of up to one sample per second, with options for frontend automation. The enhanced sensitivity of the combined system allows researchers to work with smaller protein quantities in high demand screening and drug development workflows.

SCIEX
sciex.com

Freeze and Thaw Biocontainers

Meissner has expanded its TepoFlex® biocontainer platform to support freeze and thaw operations, extending its use in drug substance storage, transport, and process integration. Built on the same film technology used across the line, the biocontainers are engineered to maintain reliability and integrity throughout demanding freeze/thaw cycles. Available in sizes from 50 mL to 10 L, the single use format integrates easily with existing infrastructure and is compatible with a range of freezer types, including blast and vertical plate systems.

Meissner
www.meissner.com

Cryostat Platform for Accelerated Histology Workflows

Leica Biosystems has introduced the Leica CM1950 Cryostat with DualEcoTec Cooling System, designed to speed specimen preparation while improving sustainability and operator comfort. The system delivers faster specimen and chamber cooling, supports temperatures down to –50 °C, and reduces energy use through a next generation refrigerant. Lower heat emission, reduced noise, and ergonomic updates further support consistent sectioning in high-throughput histology environments. The platform is intended for *in vitro* diagnostic use.

Leica Biosystems
www.leicabiosystems.com

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PLENARY KEYNOTE SPEAKERS

Timothy Yu, PhD
Boston Children's Hospital

Brenda Bass, PhD
University of Utah

Debra Miller
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Weimin Wang, PhD
Sanegene Bio

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