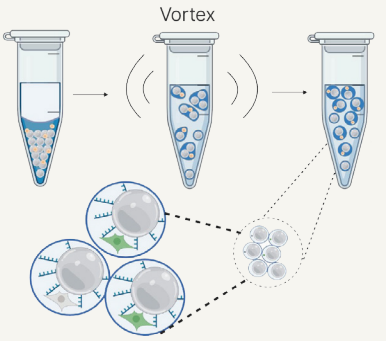
GEN Genetic Engineering & Biotechnology News

JUNE 2026

Simplifying sequencing with Illumina Single Cell Prep

The key to the new, straightforward Illumina Single Cell Prep lies with our pre-templated instant partitions (PIPs) isolation technique. Unlike microfluidic methods, where water-in-oil droplets are created sequentially, Illumina Single Cell Prep uses a vortex to gently capture all cells simultaneously in PIPs. Each PIP contains templated particles with unique barcodes for the identification of cells after sequencing, and simultaneous capture helps maintain the integrity of your sample by synchronizing capture time points across all cells.[1] Built for flexibility and requiring no specialized instrumentation, this approach ensures compatibility with organoids, complex tissues, and diverse cell types beyond single nuclei or uniform shapes. This flexibility enables a wide range of applications, from cancer cell heterogeneity analysis to drug response characterization. Illumina Single Cell Prep is reagent-based, so the number of droplets easily scales with the quantity of template particles added and kits are pre-portioned to support as few or as many cells as you need to sequence.

Using vortexing alone, Illumina Single Cell Prep isolates single cells with barcoded template particles



There are many benefits to this method, including:

5×

Value: For the same price, you can process 5X more cells using Illumina Single Cell Prep than the leading single cell alternative[2]

Scalability: Kit sizes scale with your experiment, providing a 75% capture rate and exceptionally low multiplet rate (2–8%)[1]

Flexibility: Compatible across species, with many different cell types, and from both fixed and frozen samples[1]

1. Fontanez KM, Agam Y, Bevans S, et al. Intrinsic molecular identifiers enable robust molecular counting in single-cell sequencing. BioRxiv. October 5, 2024. doi:10.1101/2024.10.04.616561
2. Illumina Research and Development

> There are a lot of researchers who will now be able to actually complete projects that they've wanted to do for years and have never been able to do because it's just not in the budget.
>
> **Jamie Padilla**
> University of New Mexico

Illumina Single Cell Prep is compatible with Illumina sequencers

MiSeq™ i100
For up to 5,000 cells

NextSeq™ 2000
5K – 90K cells

NovaSeq™ X
80K – 1.3M cells

62%
lower cost*

2X
faster sequencing**

3X
higher analytical accuracy***

* When sequencing with NovaSeq X
** Available in cloud with DRAGEN v4.5 launch
*** With the NovaSeq X 25B flow cell compared to the S4 flow cell on the NovaSeq 6000

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GEN Genetic Engineering & Biotechnology News

JUNE 2026

Next Generation Biopharma Innovation

A-List Top 10 Biopharma Clusters 2026

Protein Degradation
Broadens Scope

Organ Chips
Sees Hurdles Ahead

Mass Spec
Transforming Drug Discovery

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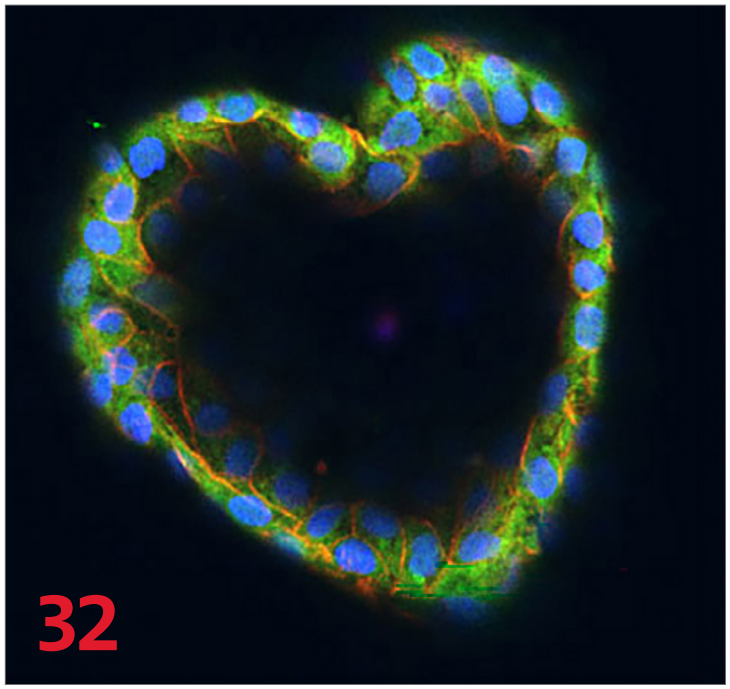
Contents

JUNE 2026 • Vol 46 • Number 6

GEN

Cover Story DRUG DISCOVERY



32

The Convergence Zone in Preclinical Research

In a quest to provide more relevant translational data, traditional *in vivo* models join forces with new approach methodologies.

A-LIST

14

Top 10 U.S. Biopharma Clusters 2026

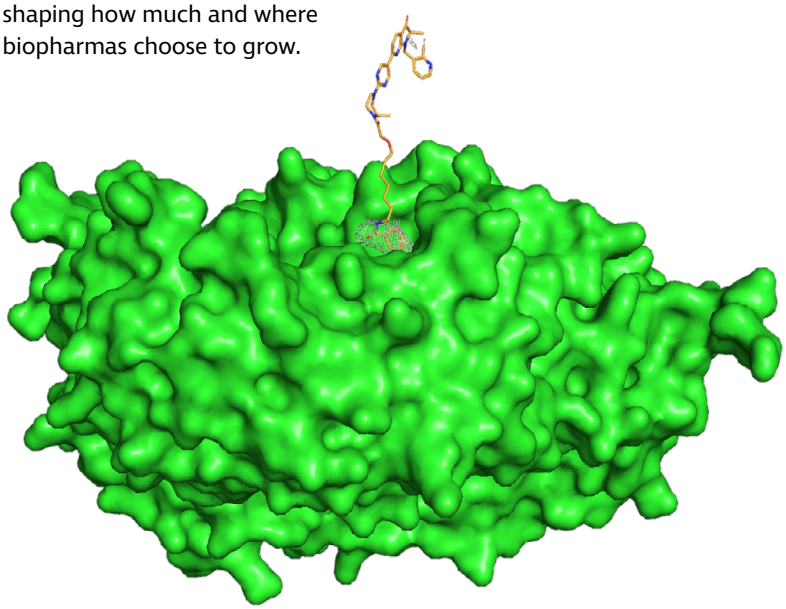
Mid-cap buyers, improved capital raising climate, and reshoring of manufacturing are shaping how much and where biopharmas choose to grow.

DRUG DISCOVERY

18

Targeted Protein Degradation Broadens Its Scope

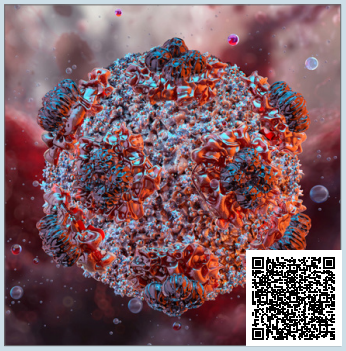
New tools and data strategies are shaping the next phase of drug discovery.



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

Heather Kowalski]

Genomics Pioneer and Life Sciences Entrepreneur J. Craig Venter Dies at 79



Hantavirus [quantic69 / iStock / Getty Images Plus

Hantavirus Vaccine Enabled by High Resolution Structure of Glycoprotein

ASGCT

ASGCT 2026: Rare Instance of AAV Integration into Human Genome Linked to Brain Tumor

24

Organ Chips Move Toward Mainstream Drug Development, with Hurdles Ahead

From spaceflight to high-throughput studies, evidence supports greater use of organ chips, but regulatory ambiguity and reliance on animal models slow adoption.

Cover Image: MilliporeSigma, the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany

Contents

GEN

DRUG DISCOVERY

OMICS

DEPARTMENTS


Manufacturers of the Highest Quality
Proteins, Antibodies & Reagents
For Research & Diagnostic Applications
CANCER MARKERS
CARDIAC MARKERS
HUMAN HORMONES
METABOLIC MARKERS
PLASMA PROTEINS
SCRIPPS
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From the **Editor in Chief**

"Much of the genetic data derived from the genome is misleading or just wrong."

—J. Craig Venter, PhD

John Sterling

The above quote appeared in the last article Venter ever penned for *GEN* in our June 2025 issue celebrating the 25th anniversary of the completion of the Human Genome Project ("J. Craig Venter Describes a Human Genomics Revolution Still In Progress"). It reveals much of the essence of Venter's personality, which combined scientific genius and verbal bluntness to the point of his being considered one of the most controversial investigators in the history of biotechnology.

Venter, who died last month at 79, was *THE* driving force behind accelerating the research that finally led to the decoding of the human genome. He was one of the most fascinating people and scientists I have personally known during my 42 years as *GEN's* editor in chief.

Venter was associated with one of the Mary Ann Liebert journals, *OMICS: A Journal of Integrative Biology*. He would sometimes call about a research finding being published in the journal and suggested that *GEN* might want to consider covering the study from the perspective of potential applications. As he focused his research on the human genome project through virtually all the 1990s, *GEN* would interview him as the project progressed and invite him to contribute an article when he could.

He was not only a brilliant and innovative scientist but also an entrepreneur who co-founded several companies. Earlier this year, he invited me to visit the J. Craig Venter Institute where he would talk about the new advances in genomic research. To my deep regret, that visit to interview him again will never take place.

Sadly, the Venter Institute reported that he died from unexpected side effects of a cancer therapy he was receiving. That is the ultimate tragedy for his family, fellow researchers, and those of us privileged to know and work with him when we could.

Venter, who was sometimes referred to as a swashbuckling pioneer, often took on the scientific orthodoxy, with critics accusing him of hype and going overboard on privatization. To many, he was a visionary focusing on technological acceleration and blending academic science with the zeal of an entrepreneur. Supporters saw him as a trailblazer who sped up genomics research by years.

Venter will certainly be missed by all who worked with or came to really know him. As his biotech legacy grows in the years ahead, I venture to say that even some of his faultfinders will wish he were still around.

Mark Wilson/Newsmakers/Getty Images

J. Craig Venter
1946–2026

John.Sterling@sagepub.com

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Mary Ann Liebert
A Part of Sage

Sticky ends

Good Vibrations: Rain Sounds Shake Seeds Awake

If you have a green thumb, you know what makes your plants grow faster and how important environmental conditions like water, pH, temperature and light are. But what about sound? Researchers at MIT found that the sound of falling droplets stimulated rice seeds to germinate at a faster rate compared with seeds that were not exposed to the same sound vibrations.

Chadchai Ra-ngubpai / Getty Images

The team's findings, published in *Scientific Reports*, are the first direct evidence that plant seeds and seedlings can sense sounds in nature.

The team developed a hypothesis to explain how the seeds might be doing this: When a raindrop hits the surface of a puddle or the ground, it generates a sound wave that makes the surroundings vibrate, including any shallowly submerged seeds. These vibrations can be strong enough to dislodge a seed's "statoliths," which are tiny gravity-sensing organelles within certain cells of a seed. When these statoliths are jostled, their movement is a signal for seeds and seedlings to grow and sprout.

"What this study is saying is that seeds can sense sound in ways that can help them survive," says Nicholas Makris, PhD, a professor of mechanical engineering at MIT. "The energy of the rain sound is enough to accelerate a seed's growth."

Like Mother, Like Yawn

Yawning begins early in life—even before birth. Yawning in the womb is thought to be a part of the normal maturation of the fetal nervous system. Yawns help babies practice coordinated movements while still in the womb. But a new study suggests yawning before birth may also be influenced by a mother's behavior.

Using ultrasound recordings of fetal facial activity, researchers monitored fetal facial movements. When the researchers used controlled prompting of the mother to yawn, they found that fetuses yawned more often after their mothers yawned, but not during non-contagious conditions used as controls. The timing and movement patterns of the yawns were also strikingly similar between mother and fetus.

Luka / Getty Images

The findings, published in *Current Biology*, suggest that babies may begin responding to and syncing with their mothers' behaviors before they are even born. Researchers say this early "behavioral resonance" could help lay the groundwork for social bonding, communication, and emotional connection after birth.

Solomon Hendrix

The Early Bug Gets the Microbe

For leaffooted bugs (*Leptoglossus zonatus*), which undergo five juvenile stages (instars) before reaching adulthood, symbiotic microbes facilitate and promote growth. After nymphs hatch in the tree canopy, where bacterial symbionts are scarce or absent, the bug must make the dangerous journey to the ground. Although risk of predation is high, failing to acquire the symbiont is lethal in the species.

A team from the University of Arizona suggests that acquisition of the bacterial symbiont *Caballeronia* is time-restricted. If the bugs don't make it in time, the result is reduced survivorship, reduced adult weight, and increased development time to adulthood.

For their study, published in *Frontiers in Microbiology*, the team tested how delayed symbiont acquisition impacted bugs. Upon reaching the second instar, nymphs were fed *Caballeronia* either on the day of their molt or every four days after. Ingesting the symbiont on day zero or four days later meant similar survival rates—around 86% and 89%, respectively. Survival rates declined after eight days (63%) and plummeted after.

"When leaffooted bugs reach the second instar, a timer starts for symbiont acquisition," explains Liam Sullivan, a PhD student at The University of Arizona. "As it becomes critical that bugs find the symbiont, it becomes less likely that if they do find the symbiont, ingestion will result in colonization and survival."

ASGCT 2026 Catalyst Award winners. From left to right: Rebecca Ahrens-Niklas, MD, PhD; Kiran Musunuru, MD, PhD; Sadik Kassim, PhD (Danaher Corp.); Fyodor Urnov, PhD; and ASGCT president Terry Flotte, MD. [ASGCT]

"It Was Not a Cure"

Musunuru Cautions ASGCT on Baby KJ Promise

BOSTON – When Kiran Musunuru, MD, PhD, walked to the microphone to deliver remarks on behalf of the team that won the American Society of Gene and Cell Therapy (ASGCT) 2026 Catalyst Award, most of the thousands of attendees surely expected a feel-good speech.

After all, it was 12 months ago that Musunuru, addressing the same convention in New Orleans, shared the exciting news regarding the delivery of a bespoke base editor to an infant, Baby KJ, with a rare urea cycle disorder. Musunuru and his colleague, Rebecca Ahrens-Niklas, MD, PhD, were recently named to the *TIME* 100 Most Influential People of 2026. "A decade from now," stated Nobel laureate Jennifer Doudna, PhD, "their names will be in medical textbooks, not only for Baby KJ, but for opening the door to personalized genetic medicine for thousands of children after him."

Musunuru and Ahrens-Niklas, from the University of Pennsylvania and Children's Hospital of Philadelphia (CHOP), respectively, were honored alongside Doudna's colleague Fyodor Urnov, PhD (Innovative Genomics Institute) and Danaher Corporation, for building the remarkable academia-industry consortium that designed and delivered the gene editing therapy, resulting in Baby KJ's discharge from CHOP and a wave of national television appearances.

Indeed, Musunuru opened his ASGCT remarks in upbeat mood. "The potential is there to [deliver personalized therapies] over and over again for hundreds of diseases centered in the liver." But halfway through his speech, Musunuru's tone changed. While most grateful for the recognition from ASGCT, he said it was important to always "be your own worst critic."

"I'll be brutally honest," Musunuru said. Despite the unquestionable "enthusiasm and excitement" surrounding the Baby KJ story, "there are some profound limitations. It was not really science at all!" Musunuru continued. "It was not a clinical trial. It was not clinical research. It was not a cure."

One Antibody, Fewer Scientific Surprises

Why maintaining translational continuity across preclinical research models can make or break confidence in experimental results

In biomedical research, promising programs rarely collapse for lack of scientific ambition. More often, they collapse under the weight of inconsistency. One assay produces compelling results, the next model delivers confusion, and suddenly, researchers are left wondering whether the biology changed or whether the tools did.

That uncertainty sits at the heart of translational continuity, a concept gaining increased attention as drug-discovery pipelines become more complex and expensive. According to Cody Spencer, PhD, Director of Scientific Affairs at Bio X Cell, maintaining continuity across experimental systems is less about rigidly replicating conditions and more about reducing unnecessary variability.

"I define translational continuity as the ability to study the same underlying biology as you move from early discovery into more complex preclinical models without introducing unnecessary variability," Spencer explains.

In practice, translational continuity means researchers can move from *in vitro* assays to organoids to *in vivo* mouse models while remaining confident that their findings reflect real biological phenomena, not artifacts created by inconsistent reagents or shifting methodologies. That distinction matters more than many researchers realize.

The greatest threat to continuity, Spencer argues, is often surprisingly mundane: switching antibodies or suppliers midway through a research program. Even antibodies marketed against the same target protein can behave differently depending on clone selection, sequence, production methods, formulation, or purification standards. When an antibody's functional profile—whether blocking, agonistic, or depleting—is well characterized, researchers can select tools aligned with their experimental goals from the start, reducing the need to switch reagents mid-program. "When you switch suppliers, you're often introducing a new variable without fully realizing it," Spencer says.

Those differences might seem subtle initially, but they can snowball dramatically in translational studies. Inconsistent potency, altered dose responses, or unintended immune engagement can suddenly emerge even when earlier experiments appeared rock solid. Researchers then face a dangerous interpretive trap: Are they observing a genuine biological effect or merely the consequences of a reagent change? "That's where you start to see promising early data that doesn't hold up in more complex models," Spencer notes.

The consequences extend beyond scientific frustration. Failed translation burns time, funding, and institutional confidence. Entire programs can stall while teams attempt to reconcile conflicting datasets generated by technically different reagents presenting as equivalent tools. For companies operating in high-stakes therapeutic areas like immuno-oncology, autoimmune disease, and inflammatory disorders, that level of ambiguity can become extraordinarily expensive.

The formulation of antibodies also plays a surprisingly large role in reproducibility, particularly *in vivo*. Preservatives, endotoxin contamination, and formulation inconsistencies can introduce unintended biological effects that distort experimental outcomes. "For *in vivo* studies, antibodies need to have ultra-low endotoxin levels and be free of preservatives to avoid introducing unintended biological effects," Spencer explains.

This emphasis on reproducibility has reinforced the case for recombinant antibodies, which are derived from defined sequences rather than traditional hybridoma methods. Recombinant production offers stronger lot-to-lot consistency and allows researchers to better control host species, isotype selection, and Fc functionality.

That predictability becomes even more critical as antibody engineering grows more sophisticated. Bispecific antibodies, for example, can engage two targets simultaneously, enabling researchers to model increasingly complex biological interactions. But those advanced formats also amplify the risks associated with inconsistency. "Small changes can significantly impact activity," Spencer warns.

Ultimately, translational continuity is about preserving confidence. In an era where reproducibility concerns continue to challenge biomedical science, researchers are increasingly recognizing that experimental reliability depends not only on biological insight but also on the consistency of the tools used to generate it. "When translational continuity is strong, the data become much easier to interpret," Spencer says. "If the biology is real, it should carry across systems." ■

"The best we can say is we hope we've turned a devastating disease into a milder, manageable condition. But it's too early to say that… This was a personalized N-of-1 therapy—we can't say what this means for anyone."

Drawing applause from the audience, Musunuru pushed on: "We mustn't be snake oil salesmen or give false hope… We have a profound ethical responsibility not to mislead families over what is possible."

"We don't actually know anything," Musunuru said. "We need to do clinical trials—scientifically and ethically."

The path forward

Musunuru set the Baby KJ story in the broader context of his group's work on phenylketonuria (PKU), one of the classic inborn errors of metabolism. A few years ago, Musunuru and Ahrens-Niklas set about designing gene editing therapies targeting the first and sixth most common PKU mutations using adenine base editors. (There are more than 1,000 known mutations that cause PKU.)

After testing in humanized mouse models, the researchers were delighted to see the phenylalanine levels rapidly drop to normal, sustained for the lifetime of the mice. Flush with funding from the Somatic Cell Genome Editing program at NIH, Musunuru and Ahrens-Niklas began talks with the U.S. Food and Drug Administration (FDA) in February 2024 to settle the question: Do we need separate Investigational New Drug applications (INDs) for each PKU variant?

"It is basically the same drug, the same gene, the same disease, the same clinical endpoints. Can't we cover both variants in a single IND and a single 'umbrella' clinical trial?" summarized Musunuru. The answer was "maybe"—the agency needed to consider the full implications of the proposal.

The Philadelphia team began to develop workflows for four more PKU mutations, leading them to propose an umbrella trial for a revised total of six variants. Following another meeting with FDA officials in early 2025, the response was extremely positive: a single IND application would be appropriate, with a single toxicology study conducted in a single species. The FDA also agreed to consider additional variants.

In parallel, Ahrens-Niklas and Musunuru were studying sick patients with urea cycle disorders. Although these are liver disorders, "the real harm happens in the brain," Musunuru said, resulting from toxic levels of ammonia. Enter Baby KJ's diagnosis with CPS1 deficiency, and the notion that there was chance to design a personalized therapy.

In the Fall of 2024, Musunuru and Ahrens-Niklas held a pre-IND meeting with FDA officials. The idea was to streamline applications for a group of urea cycle disorders caused by mutations in seven different genes.

The FDA judged that all seven therapies could be evaluated in a single Phase I/II trial, but separate INDs would be required for each gene. "We'd have to do it piece by piece," Musunuru said. First, file a master protocol for urea cycle disorders; after that IND clears, then file additional gene-specific INDs and amend the original IND.

"This is how we can make the trial accessible to all UCD patients across the country," he said.

Back to the future

Coming back to the present, Musunuru stated that although the primary IND had been filed, "this does not mean the trial is open or we can enroll patients." Musunuru listed three major issues:

- The team has not yet manufactured any gene therapy product.
- As seven INDs are needed to fully open the clinical trial, it will be well into 2027 until all INDs are submitted.
- In February 2026, the FDA issued a draft Plausible Mechanism Framework. Musunuru's team held another pre-IND meeting with the FDA to advocate for the use of prime editing for urea cycle disorders. After all, Musunuru reasoned, why should therapies be restricted to base editing approaches (G-to-A substitutions) but not patients who harbor a G-to-C mutation? The FDA indicated that a separate IND/BLA would be needed for each gene, and that process validation should be finalized before any dosing of Phase II subjects.

The path forward, Musunuru said, was to adopt an adaptive, real-time clinical trial design. That involves testing therapies, then advancing therapies from proof-of-concept to the validation phase. At that point, if all goes well, they can submit a BLA. Ahrens-Niklas and Musunuru laid out more details of their approach and dealings to date with the FDA in a commentary published late last year entitled: "How to create personalized gene editing platforms."

With that, Musunuru hastily closed and exited stage left to give a keynote address at another conference across the road. GEN

Illuminating the Drug Development Path with Cell-Based Reporter Assays

Selecting and advancing drug candidates through discovery and development is a long, resource-intensive process. Demonstrating efficacy, mechanism of action (MOA), and product quality requires robust functional data.

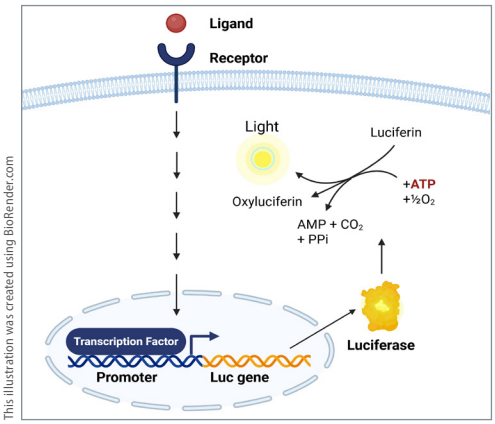
In early discovery, researchers use high-throughput screening (HTS) to identify active compounds in a biologically relevant context. During lead characterization and validation, these assays generate reproducible, quantitative data to confirm activity and support candidate selection. In later stages, cell based assays are commonly used as potency assays to ensure reliability, consistency, and lot-to-lot comparability of biologics, supporting regulatory compliance.

BPS Bioscience maintains upstream licensing agreements for its cell lines, enabling clients to operate within established regulatory frameworks. This approach mitigates downstream risks associated with third-party restrictions and supports a smoother transition from research to clinical and commercial use.

Scientific rationale for using cell-based assays in biologics development

Unlike biochemical assays, cell-based assays capture key parameters such as membrane permeability, receptor engagement, and downstream signaling in intact cells, providing a more accurate representation of biological activity. Genetically engineered cell lines include overexpression and knockout models used to validate therapeutic targets and assess compound activity. Inducible reporter assays are particularly valuable for studying signaling pathways. Luciferase reporters, placed under the control of pathway-specific response elements, enable sensitive, quantitative, and reproducible measurement of pathway activation.

Reporter systems are broadly applicable across diverse cell types and signaling pathways, supporting HTS as well as more complex applications such as research in metabolism/obesity and immunotherapy, chimeric antigen receptor and T-cell receptor functional evaluation, antibody-dependent cellular cytotoxicity assays, and other co-culture models. Many biologics, including cytokine-targeting antibodies, peptides, and mimetics, are defined by their effects on specific signaling pathways. For example, GLP-1 receptor agonists activate cAMP-dependent signaling cascades, while anti-TL1A antibodies inhibit TL1A-mediated immune signaling. Accurately measuring these pathway-specific responses is essential for candidate selection and mechanistic validation.



Activation of receptor signaling upon ligand binding triggers luciferase expression. The potency of a candidate drug can be assessed by simply measuring luciferase activity.

Applications

Reporter cell lines enable a wide range of applications:

1. **Discovery and screening**
   - Identify agonists or antagonists of specific signaling pathways
   - Screen compound libraries for selective modulators
2. **Mechanistic studies**
   - Characterize MOA
   - Analyze pathway function and regulation
3. **Functional assays**
   - Perform co-culture cytotoxicity assays to evaluate immune effector function
   - Support immunotherapy development and cell-based therapeutic evaluation

BPS Bioscience reporter cell portfolio

BPS Bioscience offers a comprehensive portfolio of pathway-specific reporter cell lines designed to support biologics development across multiple therapeutic areas. Reporter cell lines include IL-2, IL-6, and IL-15-responsive reporter cells, GLP-1-responsive models for metabolic research, and TL1A-responsive Jurkat cells.

Luciferase-based reporter systems provide rapid, sensitive, and quantitative detection of cellular responses, enabling efficient compound screening, pathway analysis, and target validation. Supporting reagents, including optimized culture media and the One-Step™ Luciferase Assay System, further streamline experimental workflows and improve reproducibility.

Advantages of luciferase reporter cell systems

- Quantitative readouts enable precise measurement of pathway activity
- High sensitivity allows detection of subtle biological effects
- Low background and high signal-to-noise ratio ensure robust data
- Compatibility with high-throughput formats supports large-scale screening

Advantages of BPS Bioscience reporter cell lines

- Optimized protocols and media simplify assay implementation
- Human cell backgrounds improve physiological relevance (with select alternative models available)
- Cost-effective workflows with minimal reagent requirements
- Extensive validation, with data often benchmarked against clinically relevant compounds
- Clonal cell lines ensure consistency and reduce variability over time

Together, cell based reporter assays and their supporting tools enable efficient, pathway relevant evaluation of biologics from discovery through late stage development. ■

Turning the Patent Cliff into a **Bioplant Opportunity**

By Gail Dutton

Using duckweed as an alternative to mammalian expression systems can ease manufacturers' transition from blockbuster to biosimilar

The 2030 patent cliff may either decimate revenue streams or provide an opportunity for innovation that can transform the biopharmaceutical industry. As it stands today, some 200 biopharmaceuticals are scheduled to go off patent during the next four years, representing approximately $300 billion in revenue.

That revenue hit can be softened if biopharma manufacturers replace traditional mammalian expression systems with a *Lemna* plant-based system. Susan Stipa, CEO and co-founder of Phylloceuticals, tells *GEN* the *Lemna* platform her team has developed can reduce operational costs by nearly 80%–90% per gram in the upstream part of the process and one-third the cost overall. That's because *Lemna*-based production lacks the 12-month lag and need for sterile growth media associated with mammalian cell lines and has less need for viral deactivation.

Susan Stipa
CEO, Co-Founder

Demonstrating those points, Phylloceuticals' *Lemna*-based approach produced microgram quantities of the PD-1 inhibitor pembrolizumab in only 16 weeks. Batch harvesting garnered "yields of approximately 0.6 grams purified mAb per kilogram of fresh weight," Stipa says.

This isn't how production has been traditionally handled, she says. So, "most companies are making defensive plays—such as mergers and acquisitions, reformulations, and reducing headcounts. But... what if the patent cliff could be an opportunity?"

The duckweed advantage

In optimal conditions *Lemna*, a genus of small free-floating aquatic flowering plants also known as duckweed, can double within 36 hours. In the wild, five to seven days is normal. "It's one of the most prolific plants in the world," Stipa points out. That rapid doubling time creates a huge speed advantage for line development and scale-up.

"Line development speed for *Lemna* is four to six months versus 18+ months for Chinese hamster ovaries (CHO) cells," Stipa says, "primarily due to *Lemna*'s genetic stability and clonal growth." It boasts inexpensive, animal serum-free growth medium, no adventitious viruses, a negative carbon footprint, and uses about 10% of the water used by CHO cell systems to produce mAbs. And, she adds, "There is near-zero impact from unforeseen environmental deviations, like power outages."

Importantly, "As a multicellular eukaryote, it possesses the advanced chaperones and complex post-translational modification machinery—specifically sophisticated N-glycosylation—required to correctly fold and stabilize large, bioactive human molecules. Our ability with duckweed to control sugars and, in particular, obtain human (or human-like) sugar profiles is what sets us apart."

Those features make *Lemna* an attractive alternative to the more expensive CHO and other mammalian cell lines. CHO cells require a very complex system, and "thousands of CHO cells must be screened to find the cell that produces the right protein and remains genetically stable. There can be genetic drift, but with *Lemna*, there is none," Stipa points out. Mammalian cells are sensitive to environmental fluctuations and require skilled technicians to manage them.

"Almost anything you can make in mammalian cells, you can make in duckweed, just a little bit better. And, yes, we do a bit better with folding," she says.

Yeast such as *Pichia pastoris* or *Saccharomyces cerevisiae* is another option, but Stipa points out, "Yeast is a story of quantity versus quality. It can produce a lot very quickly, and it does simple proteins very well, but when the protein size and complexity increase, productivity drops."

Vital SIGNS

Phylloceuticals

Location
800 N. King Street, Suite 304, Wilmington, DE 19801

Phone
484-883-88083

Website
phylloceuticals.com

Principal
Susan Stipa
Co-founder and CEO

Number of Employees
8

Focus
Developed a plant-based expression system using *Lemna* as the bioreactor that has produced a mAb in 16 weeks, start to finish.

Building where there's a need

That said, Phylloceuticals has a potentially broad client base that includes individual investigators needing microgram quantities up to contract development organizations, biosimilar manufacturers, and innovators. The company is still young, though. "We need to prove the platform is what the industry wants it to be," Stipa says.

Stipa developed a comprehensive view of the industry as a young cancer patient and through a career as a chemical process engineer who built biopharma facilities globally, and as a life sciences marketer exposed to many companies.

Her time in marketing, in fact, led to the formation of Phylloceuticals. "I had developed brand strategy for so many startups only to see the scientist-founders lose the room pretty quickly," Stipa says. "In today's media-saturated world, innovative science also needs advocates able to tell incredibly compelling stories, and to tell them so they stick."

In 2024, Stipa and her co-founders, Lynn Dickey, PhD, now chief technology and science officer, and Bill Brydges, one of the original leaders of bioengineering firm Foster-Wheeler Biokinetics, incorporated Phylloceuticals.

The company became operational in January 2025, opening its pilot facility in Rapid City, South Dakota. "Our location choice perfectly mirrors the bio-agility of our platform," Stipa says. "Traditional mammalian cell [production facilities] are often tied to very specific legacy pharma hubs. The idea of Phylloceuticals is that we can be up and running anywhere the need is, and in underserved regions. Rapid City is at the core of one of the largest rural healthcare areas [in the U.S.]."

That the facility was operational in only 12 weeks helped Phylloceuticals transition from friends and family financing to angel investment.

Initial focus: biosimilars

The company's focus on biosimilars is directly related to the patent cliff and the industry's widely discussed onshoring. The COVID pandemic highlighted a flaw in the global supply chain that left nations dependent upon others for critical pharmaceutical ingredients. Plugging that gap with the Biosecure Act (signed into law December 2025) and Federal Acquisition Regulations that ban commerce with companies of concern, Stipa says, makes Phylloceuticals an attractive choice for low-cost, onshore, mAb production. "Beyond biosimilars, we are also very active in animal health biologics and ADC/RTL support," she adds.

Regulators—notably the FDA—are familiar with *Lemna* because of its commercial-scale use for food, and for pharmaceutical products that have been through Phase II, including β-interferon, although it hasn't been used commercially for pharmaceutical products. Commercial scale has been on Stipa's mind since the beginning. "From the very early months, we had a team beginning to think about what scale-up would look like. Even when we didn't have the funds, we had advisors working on the scaleup question," Stipa says. Currently, Phylloceuticals can make microgram-to-gram quantities. Its next phase is to make gram-to-kilogram quantities.

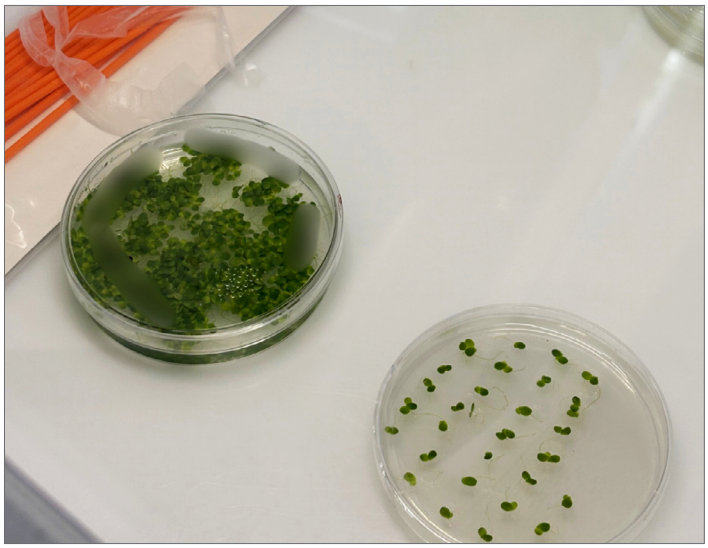
Challenges

"I think pharma rarely fails because of the science," Stipa says. She says the company is still improving extraction from the apoplast (the network of cell walls and intercellular spaces that help transport water and nutrients) and scaling to commercial quantities.

Instead, the big challenge for Phylloceuticals is simply innovating in an industry that has a legacy, multi-billion-dollar investment in stainless steel infrastructure. "Change is hard," she acknowledges. But change is also inevitable, and the biopharmaceutical industry is hardly the first to face entrenched legacy equipment and processes.

As an example, she cites Kodak, which invented the first digital camera in 1975 but didn't commercialize it. Aside from its initial technical immaturity, digital photography "would challenge the paradigm of film and chemicals Kodak sold," Stipa points out. Yet, today, more than 90% of all photos are digital, and film photography is a relatively small niche. Clearly, she says, "It is possible to shift a legacy mindset.

"Our challenge is to find forward-thinking leaders who believe the same way [we do]," Stipa continues. The first two customers have signed on—one engaged in preclinical studies around joint disease, and one focused on animal health—which suggests such leaders are there and are open to new ways of doing things. GEN



A comparative view of *Lemna* cultivation: the left plate demonstrates bulk frond growth, while the right plate shows individual fronds strategically isolated on growth media to monitor specific developmental patterns. [Phylloceuticals]

A-List

Top 10 U.S. Biopharma Clusters 2026

Abbvie, North Chicago, Il, rendering. [Abbvie]

Mid-cap buyers, improved capital raising climate, and reshoring of manufacturing are shaping how much and where biopharmas choose to grow

By Alex Philippidis

Some of the forces that shape biopharma cluster development are constants year after year, such as the emergence of startups from university and research institute labs to develop new treatments, thanks to ideas backed by the brains of researchers and executives, and the bucks of serial entrepreneurs and other investors.

But in recent years, several additional unique circumstances have come to reshape how much and especially where biopharmas choose to grow, Matthew Gardner, CBRE Americas Life Sciences Leader, shared with *GEN* recently.

One is increased acquisition of lab and manufacturing properties by "mid-cap" biopharmas ranging between $2 billion and $10 billion in market capitalization (share price times the number of outstanding shares), as they seek to better control their supply chains by maintaining their own infrastructure in evolving from research- to commercialization-focused drug developers.

"They might have been more likely to lease in a different circumstance. They've definitely caught an opportunity to jump in and take ownership. That has been an ongoing trend, and that has been true coast-to-coast in most of the major centers," Gardner said.

Among investor-owners, Gardner said, another transition has begun from pure-play biopharma real estate landlords to investors with broader portfolios encompassing healthcare—a reflection of how the two fields are increasingly converging. During December 2025 and January 2026, for example, the public real estate investment trust (REIT) Healthpeak shelled out $600 million to close on the acquisition of a 1.4-million square foot, 29-acre campus on Gateway Boulevard in South San Francisco, CA, from the nation's largest biopharma REIT, Alexandria Real Estate Equities

and BXP (formerly Boston Properties).

Those and other investors aim to cash in on the improving climate for biopharmas seeking to raise capital, from a recovering venture capital market to increased merger-and-acquisition (M&A) activity, and, in recent weeks, a revived market for initial public offerings (IPO).

Another key factor in recent cluster-building cited by Gardner is the "reshoring" of manufacturing in the U.S. by global biopharma giants, whether to satisfy growing demand for treatments—especially obesity drugs—or avoid tariffs, or both. While many of those new facilities are in manufacturing-heavy clusters like North Carolina and Greater Philadelphia, others have spread into Maryland and Virginia (the BioHealth Capital Region), and several new biomanufacturing sites have been built or are under construction in emerging clusters outside the Top 10—a trend *GEN* plans to explore in the coming weeks.

Speaking of top 10 clusters, *GEN* presents its latest edition of its nationally- and regionally-cited annual A-List of its top 10 U.S. biopharma cluster rankings, designed to show which regions are most competitive in attracting life sciences leaders, companies, and institutions. Over more than a decade, *GEN* has based its rankings on five criteria:

• ***Patents***: Figures from the Patent Public Search database of the U.S. Patent and Trademark Office, showing the number of patent families containing the word "biotechnology" and towns and cities within a given region or state.

• ***NIH funding***: Figures for NIH funding were taken from the publicly available NIH Research Portfolio Online Reporting Tools (RePORT) database for the current federal fiscal year through May 4, plus all of fiscal year 2025 (October 1, 2024, through September 30, 2025).

• ***Venture capital funding***: Figures for all of 2025 and the first quarter of 2026 as compiled by regional life sciences groups and PitchBook, which joins with the National Venture Capital Association to publish the quarterly Venture Monitor reports.

• ***Laboratory space***: The total-size-of-market figure, in millions of square feet, as furnished by regional life sciences groups. In regions that did not compile such information, the figure cited is the highest by any of several commercial real estate companies, including CBRE Group, Colliers, Cushman & Wakefield, JLL, and Newmark.

• ***Number of jobs***: The preferred sources for job figures were regional life sciences groups. Alternative sources included commercial real estate firms. GEN

To read an extended version of this story, visit
www.GENengnews.com/A-lists

RANK	AREA	NIH Funding	VC Funding	Patents	Lab Space (ft^2)	Jobs
1	Boston/Cambridge	$4.339 B	$8.44 B	29,621	63.2 M	117,108
2	San Francisco Bay Area	$3.13 B	$9.3 B	35,166	54.3 M	150,491
3	BioHealth Capital Region Maryland/Virginia/Washington, DC	$3.474 B	$1.117 B	80,808	37.2 M	135,289
4	New York / New Jersey	$4.396 B	$1.4 B	12,523	25.5 M	147,900
5	Greater Philadelphia	$1.94 B	$1.926 B	17,090	28.3 M	88,000
6	San Diego	$1.357 B	$2.4 B	18,314	28.7 M	71,448
7	North Carolina	$1.589 B	$1.877 B	5,992	18.6 M	76,000
8	Los Angeles / Orange County	$1.243 B	$0.5 B	7,211	11.8 M	155,571
9	Chicagoland	$1.607 B	$918 M	5,569	2.3 M	94,000
10	Seattle and Greater Puget Sound	$1.572 B	$1.06 B	5,416	11.5 M	48,765

PHARMA'S TRIAL PROBLEM:

Outdated Systems, Broken Data, and the **Coming AI Reset**

By Erik Terjesen

AI promises to transform clinical trials, but outdated data systems are holding it back

Erik Terjesen
Managing Director
Silicon Foundry,
a Kearney Company

Clinical development has become the most resource-intensive stage of drug innovation. Across the industry, clinical trials consume 60–70% of total R&D spending, a proportion that continues to rise as trials grow more complex, more data-heavy, and more operationally demanding. The irony is that while science has advanced dramatically, the underlying model for running trials still reflects assumptions from a pre-digital era. The result is an ecosystem in which timelines stretch, costs multiply, and meaningful efficiency gains remain elusive.

AI has reached a level of maturity capable of reshaping this landscape, but its potential remains constrained by a fundamental issue the industry has been slow to confront. The data used to power these systems was never designed with AI in mind. In fact, the true crisis in clinical development today is structural and deeply rooted in how trial data is organized, contextualized, and interpreted.

Why trial models are failing

Clinical trials were built for physical sites, paper workflows, and slow-moving systems. Modern trials look nothing like that. They are distributed, data-heavy, biomarker-driven, and increasingly adaptive, yet they still run on infrastructure designed for a simpler era.

For years, clinical operations have been organized around sites and checklists rather than continuous insight. Data moves in bursts, workflows remain fragmented, and systems rarely talk to one another. Precision medicine expanded what trials could ask of data, but the way trials actually operate has barely evolved.

The problem isn't only speed or scale. It's also the quiet erosion of efficiency in places trial plans rarely account for. Across the industry, leaders describe a growing layer of "invisible waste": repeated handoffs, duplicative manual work, incompatible data structures, and everyday operational friction that steadily stretches timelines and drives up costs, even though it seldom appears in formal project plans.

AI changes the equation, but only if trial data can support it.

Why AI stumbles in pharma

There is no shortage of AI talent, tools, or ambition in the life sciences sector. What is scarce is data that AI can meaningfully learn from. Most early AI-for-clinical-trials initiatives failed not because the models were immature, but because the data they were fed was not curated with clinical intent.

Two challenges define this crisis:

1. General-purpose models cannot interpret clinical nuance.

Models trained on large public corpora can identify patterns, but they lack clinical judgment. If the data is unstructured, inconsistently labeled, or lacks contextual metadata, the model will draw the wrong conclusions with absolute confidence. The well-known "ruler problem"—in which an AI system learned to detect malignant skin lesions based on the presence of a ruler beside the lesion—illustrates how easily models latch onto irrelevant signals.

2. Pharma's internal data is both rich and unusable.

Organizations hold decades of trial data,

but these assets are rarely AI-ready. Different study teams, CROs, and geographies used different standards. Biomarker and imaging data are often stored in systems that cannot communicate with EDC or safety platforms. And clinical notes, PDFs, and unstructured documents require interpretation that models cannot perform without curated training sets.

AI amplifies the quality of the data it is given. If the input is clinically inconsistent, overgeneralized, or disconnected from the trial context, the outputs will be clinically meaningless.

Recognizing this, many pharmas are now investing heavily in curated internal datasets, governance frameworks, and senior AI leadership, often in the form of newly created chief AI officer roles. These leaders are tasked with not just deploying tools, but rebuilding the data infrastructure from which future AI insights will emerge.

The new AI toolkit for clinical trials

Once the data foundation is strong, AI becomes a force multiplier across the entire trial lifecycle. Several categories show particularly high near-term impact potential.

Clinical-grade language models: Purpose-built models that ingest curated internal datasets can help draft protocols, refine eligibility criteria, flag operational risks, and interpret historical trial performance. Unlike general-purpose systems, these models are tuned to reason the way experienced clinical scientists do.

Multimodal AI for patient stratification and endpoint optimization: Integrating imaging, labs, digital biomarkers, and historical trial outcomes enables more precise cohort selection and improves the likelihood of detecting true therapeutic effect. These tools help convert today's complex data streams into actionable insights.

Synthetic and hybrid control arms: While still emerging, these approaches reduce dependence on large traditional control cohorts by incorporating real-world evidence and model-generated comparators when appropriate. The result is faster recruitment and more efficient statistical design.

AI agents for operations: Operational agents can triage site queries, assist with eligibility adjudication, coordinate scheduling, and draft routine documentation. They are particularly helpful in reducing the administrative burden that slows trial execution.

The most underestimated category, and the one with the most long-term potential, is clinical-driven AI, where the model is trained to interpret clinical data the way a researcher with a PhD or a clinician would. This approach addresses the core issue of context, which is essential for decision-making in regulated environments.

From site-centric to data-centric trials

Trials are gradually evolving away from rigid site-based infrastructure and toward data-centric execution. AI accelerates this shift by enabling continuous monitoring, adaptive decision-making, and greater representation across diverse populations. The next phase of this transition requires progress in several areas:

- Reliable digital biomarkers collected via wearables and sensors that feed directly into the trial data ecosystem.
- Real-world evidence integration that allows trial designs to incorporate external data while maintaining regulatory rigor.
- Improved cohort diversity, supported by AI-driven recruitment models that identify and engage underrepresented populations.
- Always-on trial oversight, where adaptive protocols adjust based on real-time data rather than periodic interim reviews.

As these elements mature, trials will resemble dynamic learning systems rather than static sequences of predefined events.

Pharma cannot do this alone

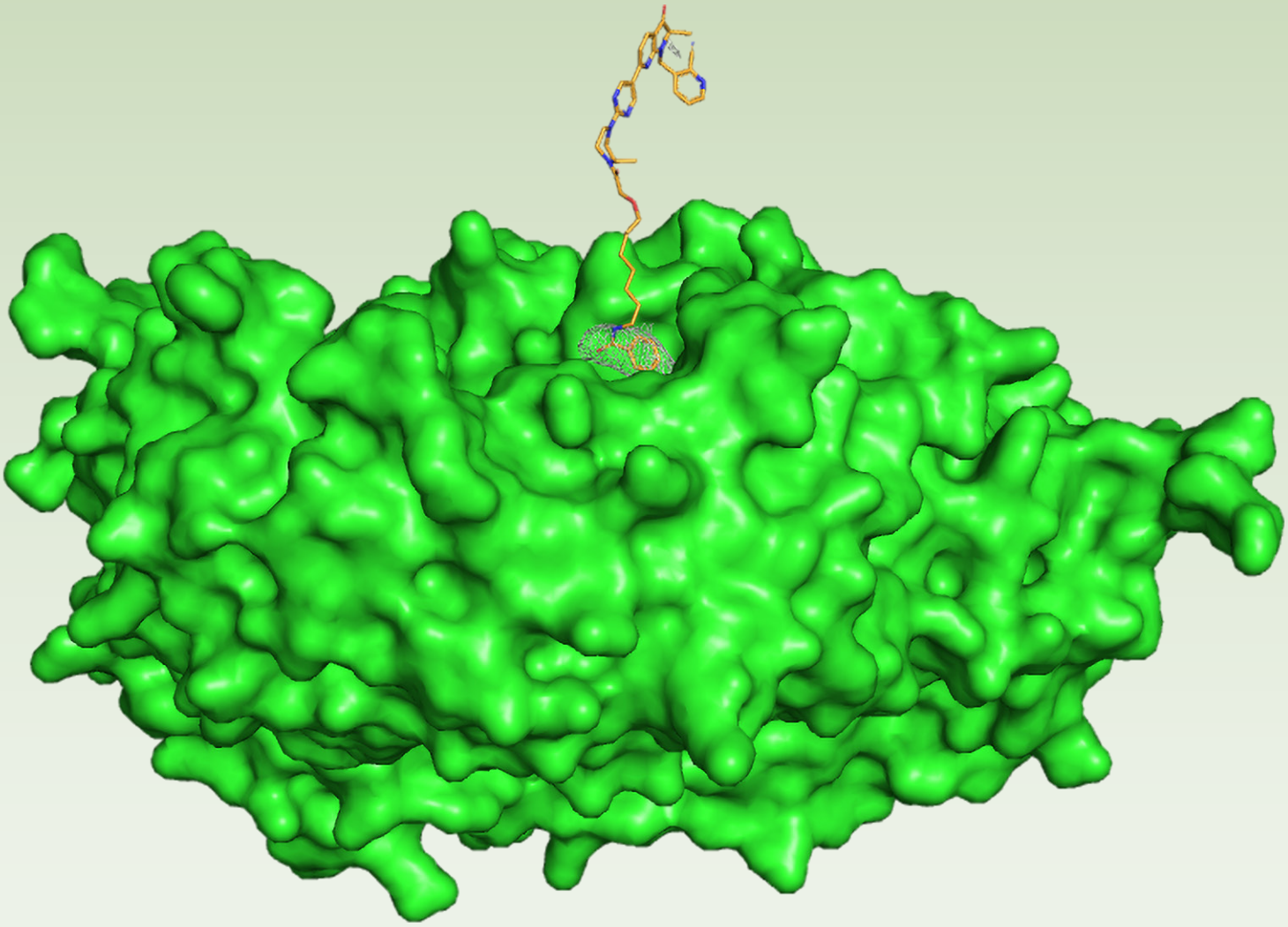
The clinical-trial innovation ecosystem is now incredibly fragmented. A myriad of startups, many founded within the last five years, are attempting to solve different slices of the trial process. Some focus on recruitment; others on protocol simulation, operational automation, predictive enrollment, or digital biomarker analysis.

This fragmentation creates noise but also opportunity. The organizations that succeed will be those that adopt a hybrid strategy, in which internal data expertise is paired with carefully selected external partners. Evaluating early-stage companies requires disciplined technical assessment and an understanding of which partners can meet enterprise requirements in a regulated environment.

Pharma organizations also face a structural talent challenge. The best AI engineers often gravitate toward startups rather than large enterprises. This dynamic reinforces the need for partnership models that combine internal governance with external innovation rather than relying exclusively on one or the other.

What AI can (and cannot) fix

While AI can dramatically shorten timelines and improve decision-making, it is not a cure-all. It will not rescue a flawed trial design, replace human oversight, or eliminate the need for regulatory rigor. What it can do is accelerate the work around those elements, optimizing how protocols are developed, how patients are selected, how data is interpreted, and how milestones are achieved. The organizations that reap the greatest benefit will be those with disciplined data stewardship and a willingness to rethink long-held operational assumptions. ■



Targeted Protein Degradation

Broadens Its Scope

New tools and data strategies are shaping the next phase of drug discovery

By Kathy Liszewski

Like any complex system, the cell depends on a tightly regulated quality control network to maintain order and prevent the accumulation of harmful proteins. This network governs protein homeostasis, including the synthesis, folding, trafficking, and ultimately the clearance of proteins. When these processes fail, aberrant or misfolded proteins can accumulate and drive disease.

Targeted protein degradation (TPD) therapeutics seek to harness this intrinsic quality control machinery to selectively eliminate disease-causing proteins. Central to this approach is the principle of induced proximity, in which a designed molecule brings a target protein into close contact with a cellular effector, triggering its removal through endogenous degradation pathways.

Two major systems underpin these processes. The ubiquitin-proteasome system governs the degradation of intracellular, soluble proteins, where targets are tagged with ubiquitin by a cascade of enzymes, including E3 ubiquitin ligases, and directed to the proteasome for destruction. In parallel, lysosome-mediated pathways handle larger, membrane-bound, extracellular, or aggregated proteins by routing them through endocytic or autophagic mechanisms for degradation.

Left. Representation of the crystal structure of Sortilin extracellular domain (green surface view) in complex with a TNFα-targeting SORTAC (orange sticks). The structure demonstrates the specificity of the interaction and enables future design of optimized degraders. [Casper Larsen, Draupnir Bio]

Building on these natural systems, a growing toolkit of TPD modalities has emerged. For example, proteolysis-targeting chimeras (PROTACs) exploit the ubiquitin-proteasome system, while newer approaches such as lysosome-targeting chimeras, including sortilin-based lysosome targeting chimeras (SORTACs), extend degradation to extracellular and membrane-associated proteins. Molecular glues, by contrast, stabilize interactions between E3 ligases and target proteins without requiring a bifunctional design, further expanding the scope of induced proximity strategies. Additional degrader technologies are being developed.

Although first described more than 25 years ago, TPD is now entering a phase of rapid maturation and increasing therapeutic relevance. By operating through catalytic, event-driven mechanisms rather than traditional occupancy-based inhibition, these approaches offer the potential to address previously "undruggable" targets, overcome resistance mechanisms, and deliver more durable clinical responses. At the same time, key challenges remain, including expanding access to extracellular targets, improving target validation strategies, and navigating an increasingly complex and data-rich development landscape.

Tackling the extracellular frontier

Early TPD efforts have primarily targeted cytosolic proteins, leaving extracellular and membrane-bound targets (estimated to comprise about 40% of the human proteome) largely unaddressed.

"Many key drivers of disease, including inflammatory cytokines, protein aggregates, and secreted factors, remain inaccessible to conventional PROTAC-based approaches," says Simon Glerup,

Simon Glerup, PhD, co-founder and CSO, Draupnir Bio and Lab: Lab photo from left: Jonas Lende, Casper Larsen, Simon Glerup, Marianne Kristensen, Camilla Gustafsen, Amanda Simonsen, Line Slemming.

PhD, co-founder and CSO, **Draupnir Bio**, a spinout from Aarhus University (Denmark).

The company is addressing this gap by utilizing its proprietary SORTAC platform, a modular, small-molecule technology designed to degrade extracellular proteins by harnessing the natural lysosomal clearance pathway. Glerup notes that "these targets are central to diseases such as neurodegeneration and inflammation, yet remain difficult to drug with existing modalities."

SORTACs are bifunctional small molecules composed of a sortilin-binding module linked to a target-binding ligand, enabling formation of a ternary complex between an extracellular disease protein and the lysosomal receptor sortilin, which drives internalization and degradation in lysosomes. Glerup elaborates, "Unlike antibody-based or intracellular TPD approaches, SORTACs combine the advantages of small molecules (such as potential oral delivery and tissue penetration) with catalytic, event-driven pharmacology. The platform has demonstrated hallmark TPD properties, including ternary complex formation and catalytic turnover, with *in vitro* and *in vivo* degradation of therapeutically relevant targets."

Glerup emphasizes that SORTACs enable degradation of both soluble and membrane-associated proteins and leverage receptor recycling to drive sustained target clearance.

The company has launched a multi-partner Danish initiative, DESYNA (Degradation of Extracellular α-SYNuclein Aggregates) in collaboration with Aarhus University, focusing on Parkinson's disease. Accumulation of α-synuclein aggregates is a key driver of disease, and the approach aims to selectively degrade these pathogenic species and halt their progression.

Glerup believes extracellular TPD represents the next major wave of innovation in the field. "By extending TPD beyond the cell's interior, the cytosol, SORTAC has the potential to unlock a large and previously inaccessible target space. With growing validation and collaborative efforts such as DESYNA, there is strong reason for optimism that this approach can deliver transformative therapies for diseases that currently lack effective treatment options."

Enabling TPD workflows

Advancing TPD depends on a coordinated ecosystem of tools that support target validation, mechanistic interrogation, and translational predictions. Within this context, attention is increasingly focused on the central challenge of translating mechanistic promise into consistent patient benefits.

Hannah Maple, PhD
Senior Director
Bio-Techne

Flavio Lima Bianchi
Lead Research Analyst
Beacon by Hanson Wade

"I think we are on the brink of seeing TPD and induced proximity truly usher in a new era in drug discovery as we await the first clinical approval of a PROTAC degrader," says Hannah Maple, PhD, senior director at **Bio-Techne®**. At the same time, she notes that "one of the challenges with this as a new drug modality is to gain a deeper understanding of where the maximum patient benefit lies from a target and indication perspective."

That uncertainty places renewed emphasis on target validation strategies. Maple elaborates, "Driving efficacy versus standard of care in a predictable way remains a challenge, despite in many cases strong mechanistic rationale for degradation versus inhibition of a particular target. For this reason, I would keep target validation high on the list of key challenges for the field as it relates to driving clinical impact and patient benefit with this technology."

To support this critical transition, Maple says Bio-Techne has established long-standing collaborations with leading research groups to co-develop new technologies and support training of the next generation of TPD scientists. The company has also built an integrated portfolio of tools spanning biological reagents, chemical probes, and assay platforms with TPD-focused capabilities across its **R&D Systems™** portfolio brand, including the **Tocris™** small-molecule products.

Maple provides an example. "Some of the most useful categories of tools for target exploration and validation in the context of TPD are the R&D Systems' Tocris Tag Degradation Platforms and self-labeling protein tag platforms." These approaches involve fusing a small protein tag to the protein of interest and pairing it with a complementary small-molecule ligand that binds the tag. The tag ligand is typically bifunctional and can be developed to recruit an E3 ligase to the protein-of-interest, eliciting degradation in a controllable, tunable manner.

Within this ecosystem, protein-level tools support target interrogation and validation. Maple highlights self-labeling tag systems as particularly valuable. "Through our R&D Systems brand, we have built a leading portfolio of these technologies, and very recently launched BromoCatch™, a next-generation self-labeling tag platform that was co-developed with [the lab of Alessio Ciulli, PhD] at the Centre for Targeted Protein Degradation, University of Dundee. BromoCatch represents a powerful, modular platform

From Discovery to Development in Emerging Modalities

ProBio is building flexible platforms for multispecific antibodies, ADCs, and other advanced therapeutic approaches

The world of biologics is moving far beyond traditional monoclonal antibodies, and companies across the biopharmaceutical landscape are racing to keep pace. From multispecific antibodies to antibody-drug conjugates (ADCs) and antibody–oligonucleotide conjugates, emerging modalities are reshaping how researchers think about therapeutic development. ProBio is at the center of that evolution.

As innovation accelerates, so do the challenges. New therapeutic formats demand not only scientific creativity, but also highly adaptable development strategies that can move quickly from concept to clinic. For ProBio, that means building flexible platforms capable of supporting the entire journey—from discovery to IND-enabling studies and CMC development.

"The emerging modalities in antibodies are being used across multiple therapeutic areas," says Jingyuan Zhang, PhD, content marketing specialist at ProBio. "So, we are looking at this entire field and the challenges that people are likely to face."

That broad perspective is becoming increasingly important as drug developers face growing pressure to optimize candidates earlier in the pipeline. According to Zhang, success with these next-generation therapies often depends on decisions made long before clinical development begins. "You need to consider early-stage design as much as possible," she adds.

That philosophy—front-loading strategy to reduce downstream risk—is a major theme in ProBio's work. Whether developing ADCs with complex linker chemistry or designing multispecific antibodies that require careful balancing of efficacy and safety, the company emphasizes early-stage planning as a critical differentiator.

This focus was also reflected in ProBio's recent presentation at the American Association for Cancer Research (AACR) Annual Meeting, where the company highlighted its integrated approach to supporting emerging modalities. The presentation underscored how early molecular design, manufacturability considerations, and translational planning can dramatically improve timelines and outcomes for developers working in oncology and beyond.

AACR served as a fitting stage for that message. As one of the leading global forums for cancer research, the conference showcased the growing industry interest in novel antibody formats and precision-targeted therapies. For ProBio, it was an opportunity to demonstrate how service providers must evolve alongside the science itself.

"The science has moved on so much that it's enabled companies to move to a modality-first approach," says Tracy Humphries, head of U.S. & E.U. regional marketing at ProBio. "Twenty years ago, it was all about just antibodies. They delivered major successes. Then we saw a fundamental rise in next-generation technologies that have opened the door for companies to look at how they can address unmet clinical needs in ways that will be more efficient or more effective than what they're using currently."

That shift creates enormous opportunity, but it also requires service providers to move faster than ever before. Emerging modalities are not static categories; they are rapidly advancing fields where platform capabilities must be built almost in real time. As Zhang says, "When a new modality emerges, we need to rapidly establish capabilities spanning discovery through IND-enabling studies and CMC development so that companies can achieve proof of concept as quickly as possible."

Rather than acting as a traditional contract development partner, ProBio sees itself as a strategic collaborator. "We aim to work with customers regardless of how their needs evolve, positioning ourselves as a collaborative partner," Zhang explains. "This approach helps accelerate proof-of-concept generation."

As the therapeutic frontier continues to expand, the companies best positioned for success will be those that can bridge innovation with execution. For ProBio, that means staying ahead of scientific trends while helping partners design smarter, faster, and with the future in mind. In the era of emerging modalities, antibodies may still be the foundation—but they are no longer the full story. ■

that uses a low molecular weight protein tag. The benefit of this approach is to minimally perturb the native localization or function of the protein being tagged, versus prior larger tags that could cause undesired functional effects."

Complementing these approaches, the R&D Systems portfolio provides targeted degradation reagents such as dTAG-13, a heterobifunctional degrader used in tag-based systems to selectively eliminate engineered proteins of interest, offering a chemical alternative to genetic knockdown approaches.

Maple reports that another impactful technology of Bio-Techne's R&D Systems portfolio is their Simple WesternTM automated western blot instruments. She explains, "TPD heavily relies on western blotting, but scaling screening campaigns using this as a primary assay is a huge time and resource drain, with variable data quality and poor reproducibility. Simple Western technology allows researchers to get reliable, reproducible and quantitative degradation data on a fully automated instrument."

Enhancing pipeline intelligence

Keeping pace with the fast-moving TPD landscape can be daunting. "Part of the problem is that reliable data is hard to come by, particularly in regards to the advancements coming out of China, with developers still relying on their own, in-house methods to generate viable, orally bioavailable lead candidates at the cost of significant time and investment," observes Flavio Lima Bianchi, lead research analyst at **Beacon by Hanson Wade**.

As evidence of this challenge, Bianchi notes that despite PROTACs comprising roughly a third of the overall TPD landscape, "to date less than five percent of PROTACs have managed to progress into the clinic and only a select few drugs have reached late-state, pivotal studies."

> **"The basic principles and technological breakthroughs that have driven TPD can be applied to targeted protein localization, stabilization, and modulation."**
>
> —Hannah Maple, PhD,
> Senior Director, Bio-Techne

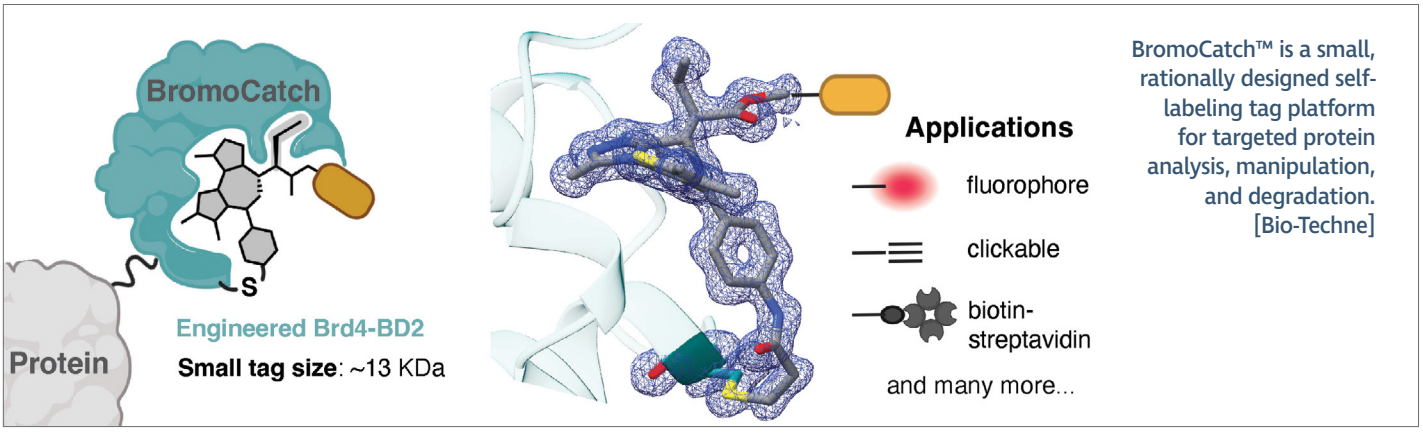
The company is addressing these limitations in several ways. "We aggregate all available TPD data and render it into an easily searchable and digestible format. Too often is information siloed within organizations and, perhaps more importantly, failed degraders are rarely published or are quietly swept under the rug."

He continues, "Beacon leverages a mixture of publicly available and proprietary data obtained directly from developers to track every single TPD program globally and to lift the lid on both the successes and the failures, enabling developers to make better, more informed decisions."

While investigators relying on in-house methods may spend significant time searching available information, Bianchi emphasizes that their platform extends well beyond data access. "Beacon TPD is a subscription-based intelligence platform, providing users the ability to search comprehensive, curated preclinical, clinical, and commercial data across the induced proximity landscape. Aside from this primary search and retrieve function, Beacon's additional functionalities include analyst reports, conference summaries, weekly newsletters and alerts, all designed to keep users abreast of the latest development within their field of interest."

Broadening TPD horizons

Bio-Techne's Maple envisions TPD expanding well beyond its original scope. "I think about TPD as one portion of a broader induced proximity revolution. The basic principles and technological breakthroughs that have driven TPD can be applied to targeted protein localization, stabilization, modulation, etc. This opens new optionality from a therapeutic standpoint and is also opening entire new fields of basic research enabled by these new principles and chemical tools." GEN



BromoCatch™ is a small, rationally designed self-labeling tag platform for targeted protein analysis, manipulation, and degradation. [Bio-Techne]

Corning Advances the Organoid Revolution

As FDA support for NAMs accelerates, Corning is helping researchers standardize, scale, and automate organoid science

The rapid rise of new approach methodologies (NAMs) is reshaping drug development, and organoids are emerging as one of the field's most promising technologies. With the FDA Modernization Act 2.0 removing the long-standing requirement for animal testing in many drug-development pathways, researchers and industry leaders are increasingly looking toward human-relevant systems that better predict clinical outcomes. Against this backdrop, Corning Life Sciences is positioning itself as a key enabler of the organoid revolution by helping scientists overcome persistent barriers related to complexity, reproducibility, and throughput.

"Corning is helping to overcome challenges to adopting NAMs such as organoid models by providing specialized consumables and reagents that are essential to generating more *in vivo*-like models," said Hilary Sherman, senior applications scientist at Corning Life Sciences. Sherman pointed to products including "Corning Matrigel Matrix, Transwell Permeable supports, and a wide variety of specialized plasticware for spheroid and organoid culture" as foundational technologies supporting the transition toward more predictive biological systems.

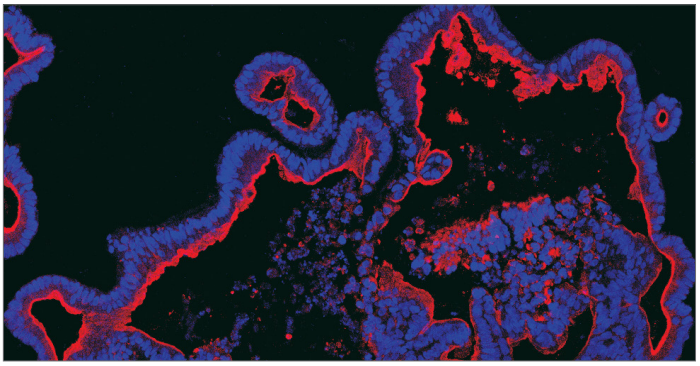
The push toward NAMs adoption gained further momentum this year when the FDA released draft guidance on alternatives to animal testing in drug development. The agency emphasized that NAMs—including organoids, spheroids, organ-on-chip platforms, and computational models—can improve predictivity while reducing reliance on animal studies.

Those priorities align closely with challenges the organoid field has wrestled with for years. During the *GEN* virtual event Spotlight on Organoids, Hans Clevers, MD, PhD, an organoid pioneer and distinguished professor at the Hubrecht Institute, stressed that standardization remains one of the field's biggest hurdles.

"We don't even have a good definition of what an organoid is," Clevers said during the *GEN* virtual event. "When is an organoid an organoid?" He added that "nothing is standardized and nothing is automated," underscoring the need for scalable workflows that can transition organoid science from exploratory academic research into robust industrial platforms.

Clevers nevertheless remains optimistic about the technology's transformative potential. "The most important part is we can now grow structures that really represent a small part of the human body," he said. "Animals are complete organisms, but they're not humans." According to Clevers, many diseases—particularly chronic human diseases—are poorly modeled in animals, limiting translational success in drug development.

Corning sees education and workflow optimization as crucial to solving



Corning

those problems. "Corning feels very strongly about supporting our customers by providing resources to educate scientists on how to create more *in vivo*-like models that are reproducible," Sherman explained. "We do this through publishing novel applications, protocols, and webinars."

The company is also helping researchers streamline increasingly sophisticated organoid workflows. "We have several protocols and optimization guides that educate customers on how to culture organoids to ensure they are set up for success," Sherman noted. "Additionally, we have many application notes demonstrating different ways of automating organoid assays to give researchers a starting point for their own work."

Automation and scalability are becoming especially important as organoids move deeper into pharmaceutical pipelines. At the *GEN* virtual event, Maya Gosztyla, PhD, co-founder and CSO of BrainStorm Therapeutics, described how her company's platform as "a very high throughput and very scalable and reproducible version of brain organoids."

Her company is studying $CDKL_5$ deficiency disorder, a rare genetic epilepsy. "The whole reason that we're doing this work in brain organoids is that the mouse models of $CDKL_5$ don't recapitulate the symptoms of the disease," Gosztyla explained.

She believes regulatory changes are accelerating industry confidence in organoid-based drug discovery. "These regulatory shifts have basically allowed drug-discovery companies to show efficacy using an alternative like a brain-organoid model," Gosztyla said, adding that such systems are "a lot more translational compared to something like a mouse."

For Corning, helping researchers achieve that translational promise means supporting every stage of organoid adoption—from foundational reagents to reproducible protocols and scalable automation strategies. As NAMs continue gaining regulatory and commercial traction, the ability to standardize organoid workflows might ultimately determine how quickly these human-centric systems become mainstream tools in drug discovery and development. ■

Organ Chips

Move Toward Mainstream Drug Development, with Hurdles Ahead

From spaceflight to high-throughput studies, evidence supports greater use of organ chips, but regulatory ambiguity and reliance on animal models slow adoption

By Uduak Grace Thomas

In April 2025, the U.S. Food and Drug Administration (FDA) released a strategic roadmap to make animal testing the exception for preclinical safety and toxicity studies within the next three to five years. Central to that vision is the adoption of validated new approach methodologies (NAMs), including organ-on-chip systems. The National Institutes of Health reinforced that shift the same month by requiring that all new notices of funding involving animal models incorporate human-focused approaches such as organ chips and other NAMs. Similar changes are emerging globally. In November 2025, the U.K. government published its roadmap to largely phase out animal testing in research while accelerating the development and validation of alternative methods.

For organ-on-chip developers, growing interest from federal agencies is a welcome trend. They are currently generating the data necessary to show that their technologies can work in stringent regulatory environments. However, there are still outstanding questions around validation standards, regulatory expectations, and how NAM data will be evaluated in submissions. At the same time, adoption remains slow, with drug developers continuing to rely largely on established animal models, which command billions in investment compared to the much smaller organ-chip sector.

Still, it is clear that momentum is building behind NAMs. And in response, organ-chip developers are stepping up to ensure that their platforms can produce results when the time comes.

From space flight to lab scale-up

When the Artemis II astronauts launched their historic 10-day journey around the Moon in April 2026, they carried some unusual cargo: organ chips containing cells from their bone marrow. The chips are part of the AVATAR (A Virtual Astronaut Tissue Analog Response) investigation, which is using organ-on-chip devices to study the effects of deep-space radiation and microgravity on human health.

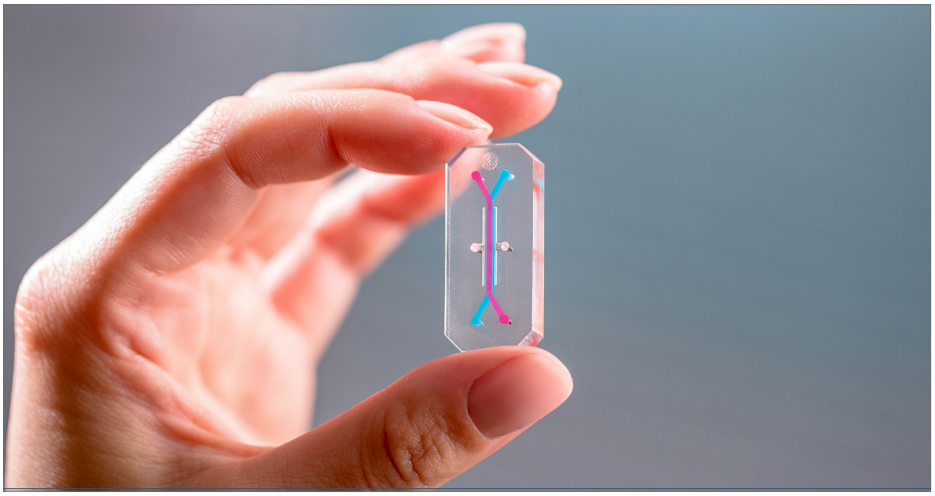
Before the trip, cells from the astronauts were harvested to create two sets of bone marrow chips: One set traveled beside the crew aboard their spacecraft, while another remained on Earth. The idea was to compare both sets of chips when the astronauts returned to Earth. More broadly, the AVATAR project also aims to provide proof-of-concept for including human organ chips in future missions.

In 2025, **Emulate** announced that its organ-chip technology was selected to accompany the astronauts on their lunar fly-by. It is an exciting project for Emulate, which commercializes human organ-chip technology developed at the Wyss Institute for Biologically Inspired Engineering at Harvard University. But it is only one of several activities that the company has been involved in the recent past. The company's liver organ chips were one of the first to be accepted for the FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) program, which supports tools that fall outside the scope of existing qualification programs but may still be useful for drug development.

In a conversation with *GEN*, Lorna Ewart, PhD, Emulate's chief scientific officer, described 2025 as a pivotal year both externally—with announcements from multiple federal agencies promising increased support for organ chips—and internally, with the launch of Emulate's new instrument, AVA, in June 2025 to address what Ewart describes as "key

Lorna Ewart, PhD
Chief Scientific Officer
Emulate

Tomasz Kostrzewski, PhD
Chief Scientific Officer
CN Bio



Above. A scientist in the lab preparing organ chips, one of the technologies increasingly being explored to reduce reliance on animal models for drug development. [CN Bio]

Emulate's organ chips played a pivotal role in the recent Artemis II lunar mission. The so-called AVATAR experiment could change how space agencies study the effects of radiation and microgravity impact human health. [Emulate]

expansion opportunities" with the company's first-generation platform. AVA has a higher throughput than its predecessor, enabling microfluidic workflows across 96 parallel organ chips or "emulations" in a single run. The company claims that it is the first organ-on-chip workstation to combine high-throughput microfluidic tissue culture with automated imaging in a self-contained environment.

Interest in the instrument to date has come primarily from large pharmaceutical companies and mid-sized biotech firms, who need to run large numbers of chips in parallel. But, Ewart says, there is also strong interest from academic institutions and government agencies. Some of that interest is driven by AVA's much smaller footprint. Compared to Emulate's first-generation system, AVA is a compact benchtop system that does not require multiple incubators. The company has also reduced the size of each emulation, or chip equivalent, by about 50%, meaning that the new platform requires fewer cells and uses less media, helping to keep experimental costs down. "Academics are actually quite excited about getting their hands on it and looking at it as a core lab instrument where multiple labs will be able to use it."

AVA also addresses concerns about reproducibility, a consistent source of worry for drug developers, and one that Emulate has made a priority. The company has shared data showing that its liver-chip biology is reproducible both internally and externally in laboratories using AVA. The company has also taken steps to minimize technical variability within experiments as well as bias when running AVA at scale. "We need to make sure that the first Chip-Array looks the same as the eighth Chip-Array," Ewart says. "If it doesn't, there's variability across those different [Chip-Arrays] that will impact the way that a user can design a full 96-emulation experiment."

More complex, automated models

When it first launched, U.K.-based organ-on-chip company **CN Bio** started with a liver-on-a-chip platform, but has since expanded to include various organ models, including intestine, lung, and kidney. The company's commercial platform is built on technology developed in the laboratory of Linda Griffith, PhD, at the Massachusetts Institute of Technology.

Currently, CN Bio has applications in multiple arenas, including safety, toxicology, and disease modeling. "For example, in the toxicology space, we have a very well-known and well-utilized model of drug-induced liver injury," Tomasz Kostrzewski, PhD, the company's CSO, tells *GEN*. That model is being utilized by several global clinical research organizations to offer assays as a service. The company also has a multi-organ system that links its intestine and liver chip models, which can be used to predict the oral bioavailability of drugs, and a range of disease models for metabolic liver disease, chronic obstructive pulmonary disease, and more.

Perhaps one of the biggest challenges, from Kostrzewski's perspective, is the misconception among some stakeholders that organ chips can fully replace animal models today. That is not a position that the organ-chip community has advocated for, he says. The focus should be on "using these tools to answer the right question and [in] the right context of use at the right time alongside all those other approaches that are out there."

Development plans in the near future involve making incremental improvements that refine CN Bio's platform over time. "One key area that we're working on is immunology and adding in more complex immune cultures into our chips," Kostrzewski says. Recently, "we presented some of the first data [incorporating] peripheral immune cells in our liver model and looking at the toxicity of monoclonal antibodies." Some customers are building "neuronal blood brain barrier models on our platform" with an eye toward "understanding how drugs can penetrate across that barrier." In parallel, the company is expanding into new organ systems, including kidney models, via partnerships.

CN Bio's PhysioMimix supports studies of metabolic liver disease, chronic obstructive pulmonary disease, and drug delivery in the brain. There are also efforts to develop additional organ systems using the technology. [CN Bio]

Evaluating CNS Anti-inflammatory Therapies with Human Brain Organoids

Inflammatory pathways involving microglia, astrocytes, and cytokine signaling are widely implicated in disorders including Alzheimer's disease, Parkinson's disease, ALS, multiple sclerosis, and traumatic brain injury. Yet despite significant investment in anti-inflammatory therapies, clinical success has remained limited.

A primary reason is that conventional preclinical models do not fully capture the complexity of human neuroimmune biology. Many therapies show encouraging results in animal studies but fail to reproduce those effects in human clinical trials.

These limitations have become increasingly problematic as evidence linking neuroinflammation to disease progression continues to grow. Genome-wide association studies have identified immune-related genes associated with Alzheimer's disease risk, while imaging and postmortem analyses have demonstrated close relationships between inflammatory activation, synaptic loss, and cognitive decline. Drug developers are therefore pursuing therapies directed at neuroimmune biology using models that lack functional human neuroimmune architecture.

CNS-3D Inflammatory Organoids, recently introduced by 28bio, is an assay-ready immunocompetent 3D brain organoid model incorporating neurons, astrocytes, and microglia to evaluate efficacy of anti-inflammatory drugs by quantifying their ability to reduce inflammatory injury, preserve tissue health, and restore neuronal network activity.

The inclusion of microglia is particularly important because it enables researchers to study inflammatory signaling within a more physiologically relevant cellular environment. Rather than measuring isolated cytokine responses in monoculture, researchers can examine how inflammatory activation propagates across interconnected neural and glial populations and how those changes affect tissue integrity and network behavior.

Data presented recently at the Microphysiological Systems World Summit demonstrated distinct cellular responses following exposure to inflammatory stimuli (*Fig. 1*) including lipopolysaccharide (LPS) and TNF-α. According to the findings, LPS exposure generated a predominantly microglial inflammatory response, while TNF-α produced stronger astrocytic activation patterns. Cytokine profiling also demonstrated measurable increases in inflammatory mediators following stimulation.

These findings are highly relevant for therapeutic development because neuroinflammation is not a single biological process. Disease states may involve different combinations of microglial activation, astrocytic dysfunction, oxidative stress, and neuronal injury.

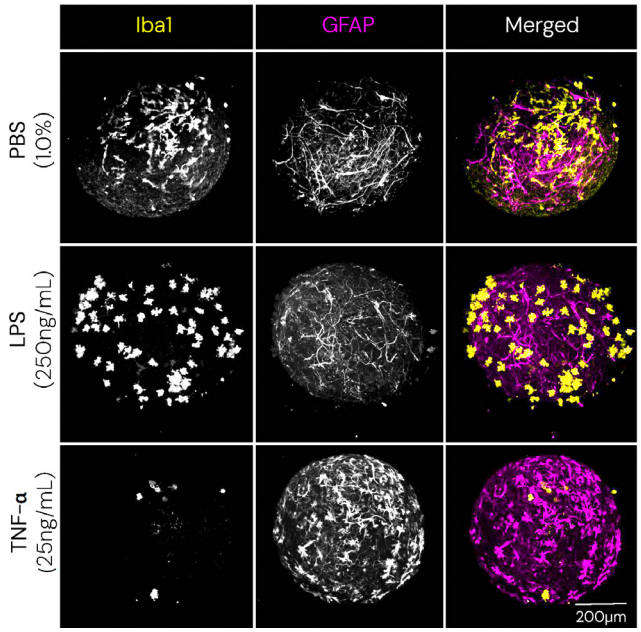


Figure 1. Differential microglial and astrocytic responses to inflammatory insults in CNS-3D Inflammatory Organoids. CNS-3D Inflammatory Organoids were treated with vehicle, LPS, or TNF-α and assessed by immunofluorescence staining for Iba1-positive microglia and GFAP-positive astrocytes. LPS induced a pronounced microglial response, whereas TNF-α preferentially increased astrocytic activation, highlighting stimulus-specific inflammatory phenotypes within the 3D CNS organoid model.

Models capable of distinguishing between these responses provide a more predictive framework for evaluating therapeutic candidates.

CNS-3D Inflammatory Organoids also support integration of functional calcium imaging with cytokine analysis, immunostaining, cytotoxicity assays, and molecular profiling. This approach addresses another persistent challenge in CNS drug development: many inflammatory assays quantify molecular markers without determining whether those changes correspond to preservation or disruption of neuronal function.

As neurodegenerative drug discovery continues to confront translational issues, interest is growing in models capable of reproducing human-specific cellular interactions and functional neuroimmune responses. Human brain organoid models help bridge the gap between preclinical findings and clinical outcomes by providing a more physiologically relevant framework for evaluating anti-inflammatory therapeutics in the CNS. ■

The company is also turning to automation to help customers scale their work. CN Bio's open design integrates well with standard robotic systems, making it well-suited for high-throughput workflows, Kostrzewski says. Customers could run more chips in parallel as part of larger screening studies with more consistency and less human intervention. There is also the potential to incorporate sensing capabilities, much like those used in biomanufacturing, to monitor system performance in real time and generate functional readouts.

In addition, the company is working to demonstrate to drug developers that organ chips can generate valuable translational data that predicts clinical outcomes. That certainly has been true for CN Bio as "we have a number of molecules that we have helped take to the clinic" that have been proven successful, says Kostrzewski. And there are customers using its organ chips "to make no-go decisions" regarding potential drug programs. "That's the ultimate proof that these technologies do what they say," he says.

Digital twin and multi-organ models

Hesperos' co-founders, James Hickman, PhD, and Michel Shuler, PhD, have been involved in the organ-chip space since its early conception. In fact, the technology that underpins the company's services emerged from work that both scientists were doing independently in their laboratories. Today, the company provides drug development services using its Human-on-a-Chip® single- and multi-organ systems in areas such as neurodegenerative disease.

In April, the company published a study in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* focused on familial Alzheimer's disease (fAD). Specifically, scientists at Hesperos and the University of Central Florida (UCF) used a neuromuscular junction (NMJ) multi-organ chip to show that fAD-associated mutations caused specific impairments in NMJ functions that occurred independently of brain pathology. Building on that work, Hesperos scientists and their collaborators are trying to understand what therapeutics could potentially be useful for both the peripheral and central nervous systems, as well as which would need to be specific for each.

James Hickman, PhD
Co-founder, Hesperos

Last year, the company also demonstrated what they claim is the first true digital twin capability using an organ-on-chip platform. That capability is described in an *Advanced Science* paper where the scientists explain how a multi-organ system comprising human liver, spleen, endothelial tissues, and blood was used to replicate the full lifecycle of *Plasmodium falciparum*, the parasite responsible for malaria. They plan to publish additional studies on their work on digital twins. Additionally, Hesperos is also participating in the FDA's ISTAND program.

In a conversation with *GEN*, Hickman described the broader adoption of organ-on-chip technology as a mixed bag, with some people being more open to the technology and others showing more resistance. He noted that many in the community are still accustomed to using animal models, which may make them more reticent to change, but also acknowledged that animal testing is a multi-billion-dollar business. "There are a lot of people with a vested interest in keeping animal experimentation going," he says. That means that although people may be interested in alternatives like organs-on-chips, from a practical perspective, it may be difficult for them to disengage from their reliance on animal models.

He also pointed to the FDA's evolving guidance on alternative technologies—and the lack of clarity—as one of the biggest hurdles. "People are still trying to get their hands around the FDA announcements on moving away from animal models," and trying to understand what the agency wants to see, Hickman explained. "We have a pretty good idea of what that [might be needed and] we work with a couple of people [to] generate data along those lines," he says. "The biggest thing is to start getting [clearer guidance] in terms of what they will accept in lieu of safety data." There are also questions around whether good laboratory practice (GLP) requirements for these new approach methodologies need to mirror those for animal studies, given the differences between the systems. "Doing GLP is really expensive," Hickman said, and requiring the same standards could effectively put many companies out of the running to conduct safety studies because they can't afford it.

Equally important is addressing the limited investment in organ chip and other alternative technologies. Hickman estimates that commercial NAM entities collectively generate hundreds of millions in revenue, compared to tens of billions secured by large animal CROs. Although federal agencies have committed to supporting NAMs, providing millions in funding, greater investment is needed for these alternative technologies to come into their own. Hickman added, "It's a matter of trying to increase that capacity to really start showing that it's a force in the industry versus a shiny new toy that people haven't quite figured out what to do with." ■

Soon…the First Organ-on-a-Chip Qualified Drug Development Tool

The Emulate Liver-Chip is in the final phases of the ISTAND drug development tool qualification to assess drug-induced liver injury (DILI)

Historical data indicate that animal models are not ideal for the determination of the efficacy and safety of human therapeutics. Ninety percent of drugs that pass animal studies do not receive regulatory approval. Improving predictive accuracy in preclinical tests is paramount, thus the movement toward more human-relevant models.

The goal to reduce the use of animals in preclinical testing changes testing paradigms. In April 2025, the U.S. FDA's *Roadmap to Reducing Animal Testing in Preclinical Safety Studies* outlined a strategic, stepwise approach to replace animal testing with scientifically validated new approach methodologies (NAMs), such as organ-on-a-chip systems, computational modeling, and advanced *in vitro* assays. FDA Modernization Acts 2.0 and 3.0 facilitated this activity by empowering the agency to accept NAMs in lieu of animal studies.

Meanwhile, legislation from the EU, Directive 2010/63/EU, requires marketing authorization holders to integrate the 3Rs (Reduction, Refinement, and Replacement) and welfare standards for the treatment of animals in all aspects of the development, manufacture, and testing of medicines. In addition, last year, the U.K. delivered an expedited phase-out plan for animal use.

But it all began in 2020 with the launch of the FDA Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program to provide a pathway to qualify novel drug development tools (DDTs) that did not fit within the agency's existing qualification programs. Qualified DDTs are defined as having a proven, specific use and can be incorporated in any drug development program for a particular context of use.

AVA™ Emulation System A high-throughput Organ-Chip platform that generates human-relevant data at scale." [Emulate]

The pilot has advanced to a permanent DDT qualification program. To date, ISTAND has accepted eight submissions–two tools that assess preclinical safety without using animals, two methods involving tissues, and one statistical approach.

The rigorous ISTAND process

In a 2022 *Communications Medicine* study to test drug-induced liver injury (DILI), 870 human Emulate Liver-Chips created with cells from three different human donors were challenged with 27 different drugs. The human Liver-Chip predicted human DILI with 87% sensitivity and 100% specificity, ~7 to 8 times more accurate than the comparable animal models.[1] These results prompted Emulate to submit a Letter of Intent (LOI) to ISTAND in 2024.

ISTAND accepted Emulate's LOI for the first organ-on-a-chip DDT to predict DILI. The human Liver-Chip S1 was proposed to assess the risk of small molecule candidate drugs inducing DILI in adults to create human-relevant data for candidate drug IND submission.

The LOI acceptance was the entry point in a three-step rigorous qualification process. ISTAND required Emulate to qualify the *in vivo*-like physiological functionality of the Liver-Chip S1, and quantify its ability to predict DILI risk through changes in tissue morphology as well as alterations in albumin and alanine transaminase (ALT) protein concentrations when the chips were challenged with toxic drugs administered across eight concentrations.

Now, the Emulate Liver-Chip S1 is in the final stages of qualification. Two independent commercial users need to successfully produce similar results. Pending successful completion, the Liver-Chip will be the first FDA-approved DDT to assess the potential of a small-molecule candidate drug to cause DILI when a prior structurally similar small-molecule has shown DILI in the clinic.

High-throughput capabilities

Moving toward reduction and, in some cases, replacement of animal models demands both biological fidelity and throughput. For model development and target validation, the Zoë-CM2® Culture Module automates the precise condition needed to culture up to 12 chips.

For high-throughput options, the AVA™ Emulation System is a self-contained Organ-on-a-Chip workstation that fuses high-throughput microfluidic tissue culture, full environmental control, and real-time imaging into a single, compact benchtop unit. The Chip-Array™ consumable integrates 12 independent Organ-Chips into an SBS format for 96-well streamlined workflows with multichannel pipettes and automated liquid handlers. ■

Reference available online.

State of the Diagnostic Industry: Recombinants on the Rise

By David A. George

How fragile supply chains have made recombinants the right choice

David A. George
Director, Product Research
Scripps Laboratories

Discovery of a fragile foundation

Four years ago in *GEN*, Scripps Laboratories predicted that the clinical diagnostic industry was on the verge of a recombinant protein revolution. At the time, *in vitro* diagnostic (IVD) assay developers were opposed to using recombinant proteins as replacements for proteins derived from human or animal tissues, glands, organs, and fluids, so-called "native" proteins. The pushback was vigorous, even palpable.

Today, the transition to recombinants is underway, as they are being approved and adopted in IVD assays around the globe. My team and I witnessed firsthand the shortage of native starting materials and helped drive this shift by developing recombinants suitable for the IVD industry. Recombinants are now the most responsible option in many diagnostic areas for laboratories that care about long-term risk management, supply chain resilience, sustainable sourcing, and price stability.

The IVD industry relied far too long on a surprisingly fragile supply network. Many of the proteins used in diagnostic assays are purified from starting materials obtained from human donors, or from abattoirs in the case of animal-sourced materials. For decades, this system appeared satisfactory: native materials were available, performance was good, and IVD assays were being produced to meet global demand. The system appeared sustainable, and there was no visible reason to change; that is, until there was.

Native sourcing becomes unsustainable

The erosion of the native starting material supply chain was not a single, isolated event. It occurred over many years, even decades. Today, native raw materials for critical proteins in several diagnostic areas are unavailable in the quantities needed to support the growing IVD industry.

Going back 10 to 15 years, human hearts and livers were becoming increasingly expensive and difficult to obtain. In addition, the quality of the donor organs made available to reagent manufacturing companies was deteriorating severely. Many organs were either resected or visibly diseased. Poor-quality hearts yielded less and less of the cardiac biomarkers creatine kinase MB (CK-MB), troponin I (TnI), and troponin T (TnT). Similarly, yields of the iron-storage protein ferritin from human livers decreased precipitously.

Pituitary glands have a similar story of declining availability and spiking costs. Pituitaries are the source of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and thyroid-stimulating hormone (TSH). These hormones are essential to testing in reproductive medicine (FSH, LH, PRL) and thyroid disease (TSH). The pituitary gland is small, the size of a pea, and each human has only one. Several thousand glands are needed, from several thousand donors, for a single pituitary gland-extraction batch. Given the growing size of the reproductive and thyroid testing markets, such large-scale consumption of this limited resource was not sustainable.

Animal-derived proteins are not immune to such supply chain disruptions. Changes in how porcine stomachs are processed at abattoirs around the world significantly reduced the intrinsic factor content available for purification. Porcine intrinsic factor has a high affinity for vitamin B12 and has been used for decades in metabolic diagnostics as the binding reagent in B12 assays. With the new stomach excision process resulting in lower yields, producing native intrinsic factor has become more challenging and expensive.

One telling indicator that some areas of the native protein model are under strain is the behavior of IVD assay manufacturers themselves. Many long-standing hormone customers have implemented a "last time buy" strategy, purchasing native hormones in quantities to last three to five years. This tactic may bridge a short-term gap, but it signals a deeper, industry-wide revelation: continuing to build assay portfolios on such vulnerable raw materials is not aligned with long-term risk management.

From skepticism to necessity

When companies began presenting recombinant alternatives to the IVD industry, the reception was cool. Many diagnostic manufacturers would not entertain a discussion about recombinants, let alone consider evaluating them. The conventional wisdom was that native proteins were inherently superior in immunoassays, particularly for structurally complex proteins, like the 24-subunit ferritin molecule, or for glycosylated, two-subunit proteins, like FSH, LH, and TSH. To be fair, the recombinants available 10 or 20 years ago were not produced with the IVD industry in mind and did not perform up to industry standards.

In only a few years, the IVD industry's attitude toward recombinants has shifted dramatically. A willingness to evaluate them as replacements for native proteins has spread across the globe. The same diagnostic laboratories that refused to have a conversation about recombinants four years ago are now proactively soliciting their suppliers for recombinant alternatives to native proteins. Many global IVD leaders have implemented a mandate to switch to recombinant proteins wherever a native protein may be considered at risk of a raw material shortage. Furthermore, when a new assay is being developed, a "recombinant-first" approach is now the norm.

We have also witnessed a cultural element to the shift. Some of the larger IVD companies have said that their scientific staff was reluctant to switch away from native proteins, but that the transition to recombinants is happening, regardless. This, too, demonstrates a broader understanding in the industry of the fallibility of the old native model.

Recombinants taking over

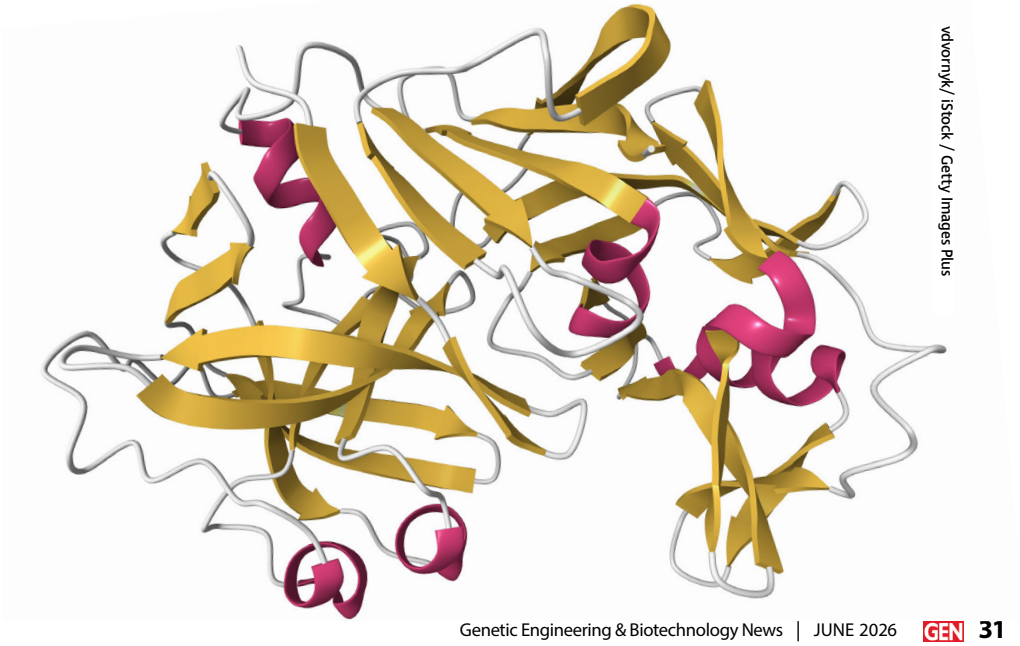
The most swift and dramatic transition to recombinant hormones is occurring in the fields of reproductive biology (FSH, LH, PRL) and thyroid disease (TSH). Historically, recombinant forms of these hormones performed poorly, so the resistance to evaluating recombinants was strong. As the supply of pituitary glands contracted, however, assay manufacturers were forced to confront the vulnerability of their supply chain. Fortunately, having inside knowledge of the pituitary supply constraints, our laboratory set out early to develop recombinant forms of these hormones. By the time the supply crisis hit, we were prepared with a full line of IVD-assay-tested recombinant hormones.

The response in the industry has been decisive and far-reaching. Most customers for native hormones have now tested, approved, and switched to recombinant versions. This change did not occur because native hormones suddenly became unusable, but because their supply became incompatible with the magnitude, reliability, and planning requirements of the industry. By contrast, recombinant hormones can be produced at scale in controlled systems with consistent quality and predictable availability.

Cardiovascular diagnostics are following a similar path. Recombinant TnI, TnT, CK-MB, and myoglobin are being adopted quickly as replacements for the native forms derived from human hearts. The supply of suitable organs cannot keep pace with industry demand, as cardiovascular disease is on the rise globally and the growth of point-of-care testing continues. Recombinant cardiac markers offer a solution to organ supply shortages, meeting the industry's high demand for these proteins, while maintaining the performance characteristics IVD laboratories expect.

In anemia and metabolic diagnostics, the switch has not been immediate, but it is underway. Recombinant apoferritin (ferritin without iron) and recombinant human intrinsic factor are available to replace the native proteins, and they are being evaluated and approved. The global supply of native ferritin and intrinsic factor is diminishing, but the situation is

See Thought Leader on page 51



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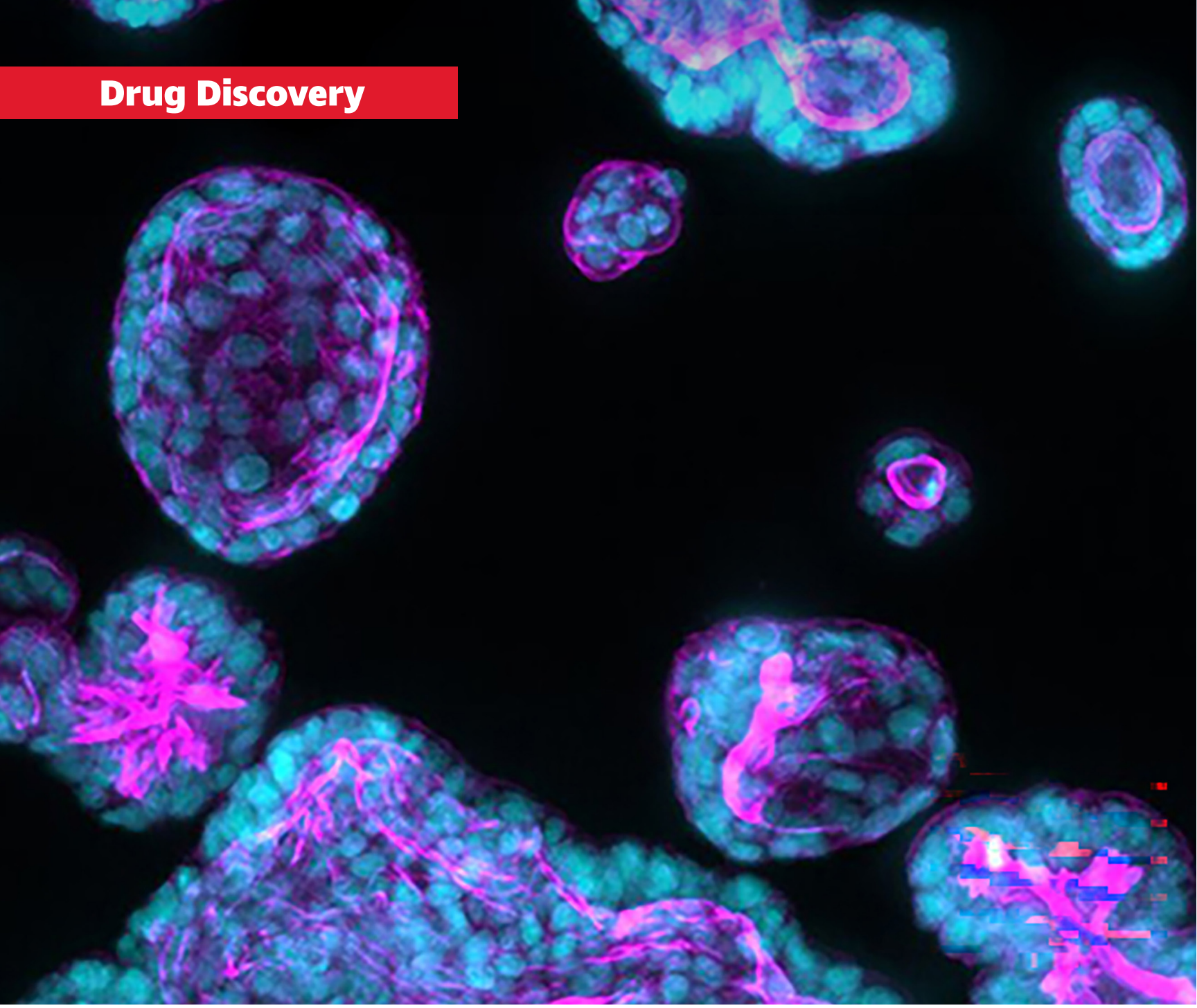


Next Generation Biopharma Innovation

By MaryAnn Labant

In a quest to provide more relevant translational data, traditional *in vivo* models join forces with new approach methodologies

Researchers are digging deeper into biology's complexity. In preclinical research, the traditional *in vivo* models are simply not enough to fuel the engine with the relevant translational data needed to progress successfully to the clinic.

As research needs evolve in immunology and immune-oncology—as focus on neuroscience increases and metabolic drugs such as GLP-1-based therapeutics become more prevalent—*in vivo* model suppliers are being requested to up the game on new platforms. In response, these suppliers are expanding their humanization platforms while developing advanced models that can be used to study complex and overlapping disease biology.

Regulatory factors also affect this market. The continued focus on the reduction of the use of animals by U.S. and European regulatory authorities has further opened the door to new approach methodologies (NAMs). NAMs are not new. Organ-on-chip or microphysiological systems, organoids, and iPSCs have been available for years. Finally, these systems are entering the limelight. Although the NAM market still requires more standardization across platforms, these systems are starting to impact preclinical research.

Building translational engines

The Jackson Laboratory (**JAX**) recently launched its latest humanized model, the NSG®-SGM3-IL15-MHC I/II DKO (S15-DKO). The S15-DKO represents their latest advancement in generating PBMC-humanized mice, supporting broad engraftment of immune cell subtypes such as CD4+ and CD8+ T cells, CD33+ myeloid cells, and CD16+/CD56+ natural killer (NK) cells. The knockout of the murine MHC Class I/II receptors delays the onset of Graft vs. Host Disease (GvHD).

The model also supports the engraftment of rare immune cell subsets, including γδ T cells and CD19+/CD38+ B cells that retain the memory state of the donor PBMCs.

Another advanced model for CD34+ hematopoietic stem cell (HSC) humanization, the NSG-FLT3-IL15 mouse generates a cellular-diverse human immune system encompassing myeloid cells, mature NK cells, functional dendritic cells, and T cells.

Both models are available in naïve strains, or off-the-shelf pre-characterized PBMC- and HSC-engraftment, along with full preclinical services tailored to immuno-oncology and autoimmune drug discovery.

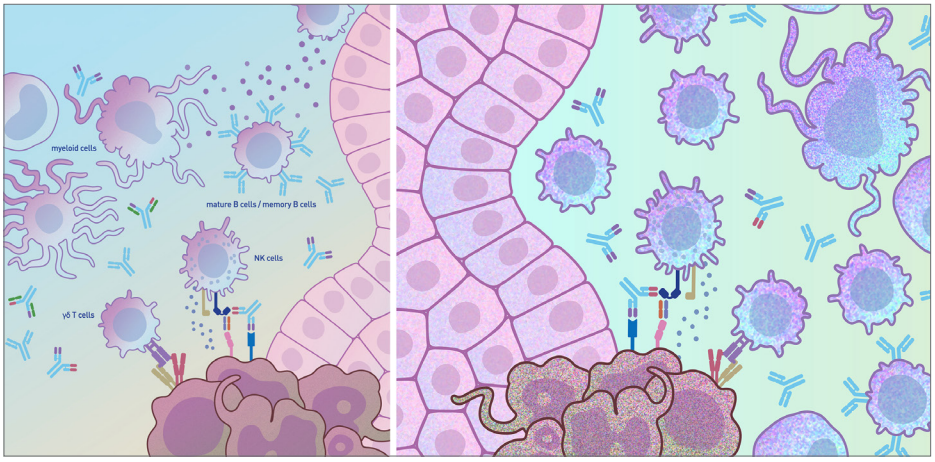
"With the FDA's renewed focus on reducing reliance on non-human primates in biologic development, demand for validated, translational preclinical models has never been higher," said Luke Dimasi, senior director, JAX.

The genetically humanized FcRn platform and the newly expanded Tg32 hALB mouse address this need. Lacking murine Fcgrt and albumin while expressing their human counterparts, the Tg32 hALB is the first model for studying the pharmacokinetics and pharmacodynamics of human albumin therapeutics, as well as human IgG and Fc-domain-based biologics. Preclinical mAb testing services are available.

"Our offering extends beyond the vivarium," Dimasi emphasized. JAX's iPSC repository continues to grow with engineered lines carrying disease-relevant mutations linked to Alzheimer's, Parkinson's, ALS, and frontotemporal dementia. In 2025, JAX added HALO-tagged and TET-inducible lines to the collection. The acquisition and integration of the New York Stem Cell Foundation (NYSCF) brings complementary patient-derived iPSCs to the portfolio.

"As the field moves towards new approach methodologies (NAMs), we are evolving alongside it," Dimasi pointed out. "Our *in vivo* mouse capabilities give us decades of deeply validated biological context. We are now layering human iPSCs and AI-computational phenotyping on top of that foundation to build a convergent

Left. Patient-derived organoids (PDOs) retain individual genetic and phenotypic characteristics.The image shows immunocytochemical (ICC) characterization of human colon PDOs that are positive for the colon-specific marker CA IV (pink), nuclei (blue). [MilliporeSigma, the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany]



S15-DKO model is JAX's latest advancement in generating PBMC-humanized mice, supporting broad engraftment of immune cell subtypes. The knockout of the murine MHC Class I/II receptors delays the onset of Graft vs. Host Disease (GvHD). [The Jackson Laboratory]

translational engine that no single approach could deliver alone."

Developing relevant models

According to Jason Rashkow, PhD, product manager for research models, **Charles River Laboratories**, the company's comprehensive collection of spontaneously developing rat models spans metabolic disease, diabetes, hypertension, and heart failure, providing strong translational relevance across cardiometabolic indications.

Custom diet preconditioning services allow researchers to tailor disease progression to specific study objectives through strategic model selection and diet design. Standardized preconditioning offerings are planned. "This approach will accelerate study initiation, giving researchers faster access to these metabolic disease models," said Rashkow.

The increasing prevalence of GLP-1-based therapeutics and next-generation incretin and poly-agonist therapies expanding into cardiometabolic indications such as heart failure with preserved ejection fraction (HFpEF) is accelerating demand for advanced disease models. The combination of established disease models, standardized preconditioning approaches, and custom solutions reflects the complexity of modern metabolic drug development.

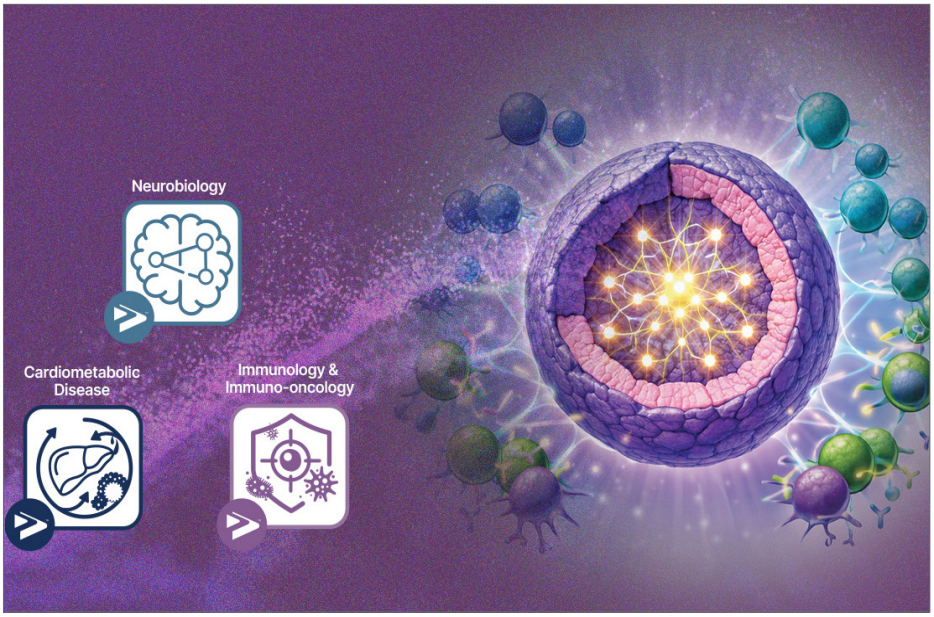
In addition, optimization of the generation of CD34+ HSC-humanized mice continues. These models, developed on the severely immunodeficient NCG strain, support research in immuno-oncology, autoimmune disease, vaccine research, and related fields.

As immuno-oncology research needs shift, so does the need for models that enable the study of NK cell-based therapies, tumor microenvironment reprogramming, and cancer vaccines. "Although variant NCG models expressing human cytokines or HLA transgenes begin to meet these needs, transgenes can influence humanization requirements," Rashkow noted.

To counteract this, the company expanded access to a peripheral blood mononuclear cell (PBMC) engrafted NCG variant strain carrying a double knockout for murine MHC class I and class II, which significantly delays the onset of GvHD, allowing for longer-term studies in the context of mature T cells.

To better support researchers studying HLA-A2-restricted immune responses *in vivo*, humanization optimization of a NCG variant expressing human HLA-A*02:01 was completed. Further development of the humanization protocols for other variant strains will support next-generation immunotherapy discovery and translational research.

Lastly, the expanded aged C57BL/6 mouse offerings support researchers investigating age-related disease. As a licensed distributor of JAX® Mice to researchers in Europe and Asia, Charles River Europe can now provide aged C57BL/6J mice up to 90 weeks of age. In North America, Charles River offers aged C57BL/6N mice up to 77+ weeks of age.



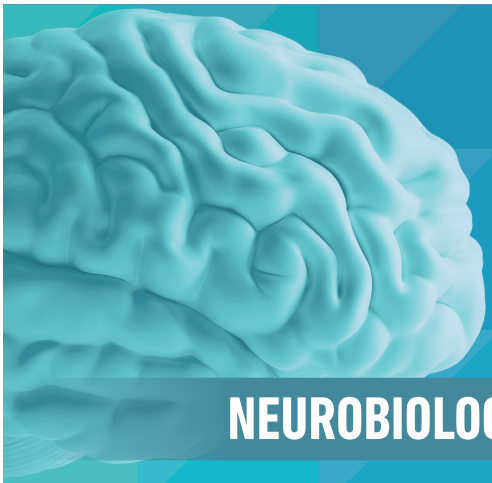
With the goal of improving translation relevance, Taconic develops *in vivo* models that reflect complex and overlapping disease biology in immunology, immuno-oncology, neurobiology, and cardiometabolic indications. [Taconic Biosciences]

Improving translational fidelity

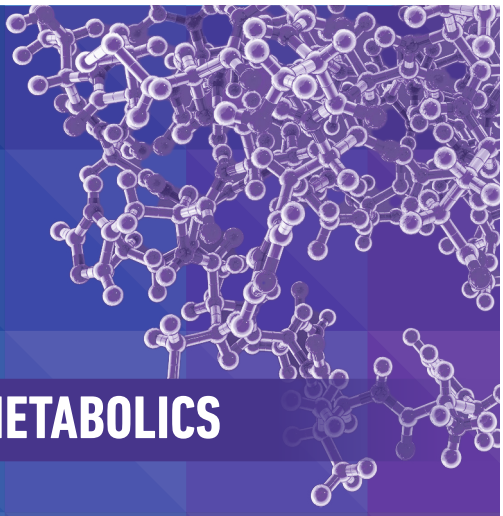
"Improved translational fidelity, increased demand for study-ready systems that better align with clinical endpoints, and the need to model complex and overlapping disease biology are driving model development," related Michael Seiler, PhD, vice president of portfolio management, **Taconic Biosciences.**

Complex modalities such as checkpoint inhibitors and engineered cell therapies require more complete immune system function and deeper phenotyping. Expansion of the FcResolv® NOG portfolio and huSelect™ services reduces murine immune interference and donor variability. Advanced flow cytometry panels support deeper, standardized immune profiling.

Planned launches include platforms and models designed to support immuno-oncology, biologics, engineered cell therapies, infectious disease, and autoimmune research, with a focus on more complete and functional human immune system biology. Gene and protein analysis



NEUROBIOLOGY



METABOLICS

THE JACKSON LABORATORY

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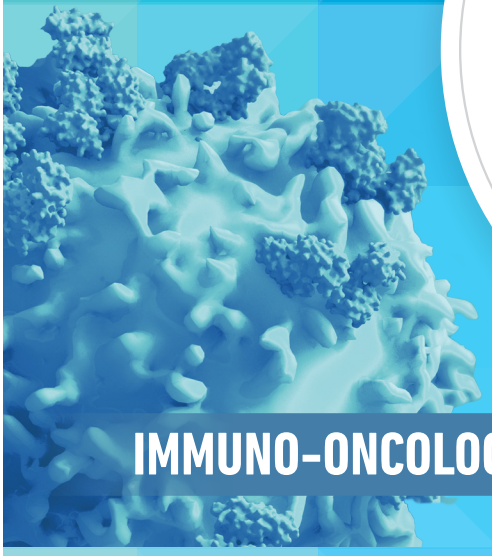

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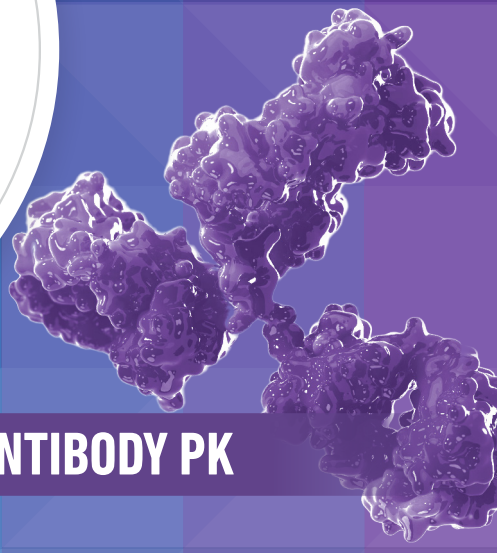

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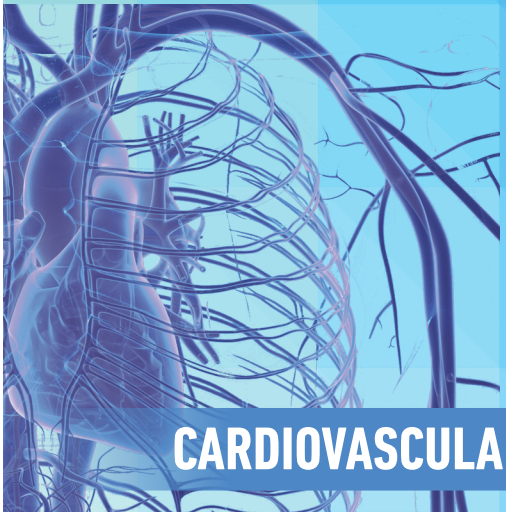


CARDIOVASCULAR

AUTOIMMUNITY

services are available.

In neuroscience, the shift is toward better alignment with clinical disease biology, particularly in Alzheimer's disease and neuroinflammation, along with increased focus on blood-brain barrier (BBB) biology and CNS delivery. Parkinson's disease model offerings include aSyn KI/KO, PINK1 KO, and LRRK2 KO rat models.

Future models include BBB-focused platforms such as TFRC and CD98, ARTE10 crosses with BBB models, and neuroimmunology-focused NOG variants, including IL-34 and TREM2-related models.

The rapid growth of obesity therapeutics, including GLP-1 and next-generation incretin approaches, is accelerating demand for more predictive metabolic and liver models in cardiometabolic disease. A range of models are aimed at obesity, MASH, cardiovascular disease, and DMPK applications.

Taconic is expanding its capabilities in transgene characterization, CRISPR off-target analysis, and tiered Custom Model Generation Solutions. The acquisition of TransCure bioServices significantly bolsters support of integrated *in vivo* study services, particularly in humanized immune system and immuno-oncology research. "We now offer a more seamless, end-to-end solution from model selection through study execution and data generation," said Seiler.

"We continue to evolve toward integrated solutions rather than standalone models. This includes expanded CMS and CMGS capabilities, humanization-as-a-service, deeper phenotyping and multiomic analysis, and partner-enabled data generation," Seiler added.

Importantly, the move toward integrating *in vivo* models with complementary technologies such as organoids, iPSCs, and AI-enabled analysis will influence how models are developed and deployed within research workflows.

Standardizing NAMs

The field is clearly shifting toward ready-to-use biology, producing a strong demand for standardized NAM platforms and services that deliver consistent, high-quality results. To facilitate scientists, **MIMETAS** continues to develop robust OrganoReady® models and advanced services, including immune-competent and vascularized systems across multiple organs.

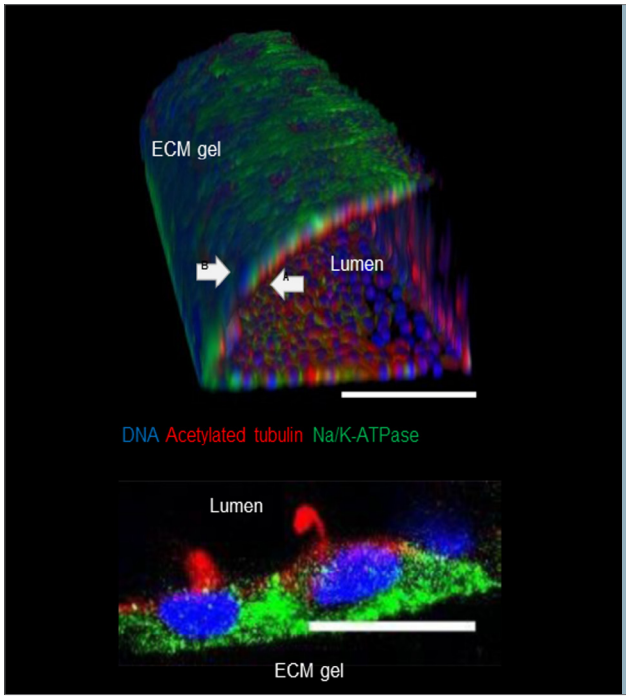
"Last year, we strengthened our fee-for-service capabilities and advanced several models to deliver high-quality biology in a consistent, scalable way," said Paul Vulto, PhD, co-CEO and co-founder, MIMETAS. "We made strong progress in our kidney tubuloid research program, CAR T-related applications, and a BBB model under unidirectional flow."

The novel human distal nephron-on-chip model in the OrganoPlate® replicates physiologic sodium and water transport using primary human kidney cells. This three-dimensional microfluidic platform, as detailed in *Kidney360*, serves as a high-throughput tool for functional drug screening and investigating distal nephron physiology and disease.[1]

In addition, a three-dimensional BBB microvasculature model developed on the OrganoPlate Graft 48 UniFlow was evaluated in a recent *Fluids Barriers CNS* publication. Tri-cultures of endothelial cells, pericytes, and astrocytes were used to demonstrate that this pump-free, unidirectional perfused, three-dimensional BBB model outperformed simpler systems on vascular architecture and barrier function. Its high-throughput nature renders the model suitable for studies of BBB function in health, disease, and therapeutic development.[2]

This year, the company's UniFlow technology will be offered for in-lab use, enabling customers to create a stable, perfusable vascularized bed for endothelial tissues. New OrganoServices for gastrointestinal toxicity (GI tox) and drug-induced vascular injury (DIVI), alongside a multi-donor expansion of the OrganoReady Colon Organoid product, are also planned.

A major trend in NAMs is the increased need for standardization and



A polarized kidney tubuloid in an OrganoPlate chip showcases apical and basolateral access. Immunofluorescence 3D reconstruction demonstrates tubule polarization and barrier formation: *blue*, DNA; *red*, acetylated tubulin; and *green*, Na /KATPase. [MIMETAS]

SPATIAL ATLASING:

Why Sensitivity Is the Real Frontier

Cell atlasing efforts rest on a deceptively simple premise: To understand a tissue, you must find every cell in it, including the rare populations and transitional states whose biology is often the most clinically meaningful.

This is where atlasing gets hard. Throughput is no longer the bottleneck. Sensitivity is. A platform that captures only a fraction of transcripts per cell fails to detect lower-abundance populations that define an atlas's resolution and utility.

A liver atlas that rewrites human zonation

A recent *Nature* study by Yakubovsky and colleagues at the Weizmann Institute illustrates what sensitivity makes possible. They built a spatial atlas of the healthy human liver from live donors, avoiding the transcriptomic distortions of deceased or adjacent-normal tissue, and used the MERSCOPE® Platform with a 500-gene panel to validate cellular zonation at single-molecule resolution.

What they found reshapes a long-standing model of liver biology. Hepatocyte functions long thought to be periportal in mammals, key urea cycle enzymes (*OTC, NAGS, ASL*), the gluconeogenic gene *PCK2*, and the master transcription factor HNF4A, are pericentrally zonated in humans. Kupffer cell localization is also inverted relative to mouse: in humans, these macrophages are enriched in the pericentral zone. None of this would have surfaced without high-sensitivity spatial transcriptomics.

"MERSCOPE allowed us to validate zonation programs at single-molecule resolution. That sensitivity was essential to a reference atlas we could trust," said Shalev Itzkovitz, PhD, an assistant professor at Weizmann Institute of Science and lead author on the *Nature* paper.

MERFISH 2.0™: built for the cells that might be missed

MERFISH 2.0 offers improvements to per-cell transcript capture and signal-to-noise that expand the dynamic range over which low-abundance transcripts and rare cell types become reliably detected. Early disease states, transitional progenitors, sparse immune subsets, and niche stromal cells move firmly into the resolved fraction of the atlas.

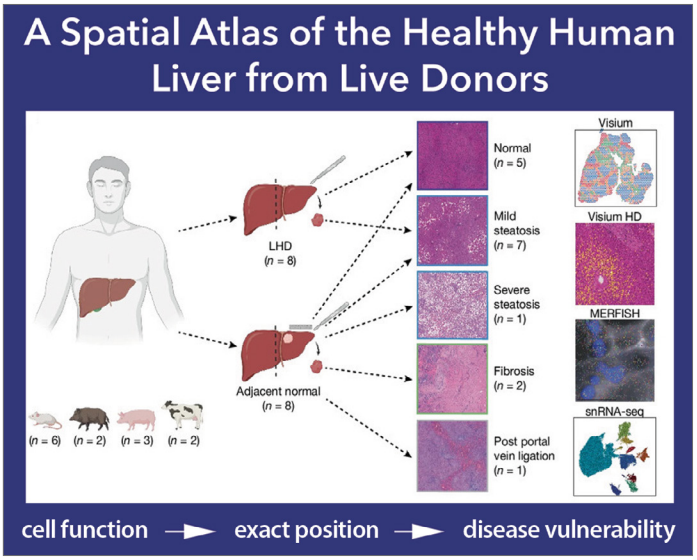
"When we set the design goals for MERFISH 2.0, the question we kept coming back to was: what are users still missing? Throughput wasn't the answer, sensitivity was. Lowly expressed genes, and rare cells are where the most important biology often lives, and MERFISH 2.0 makes sure that rare events stop being the ones that get away," said Jiang He, PhD, Co-founder and VP of Reagents, Vizgen.

Why MERSCOPE Ultra™ Platform is the spatial atlas platform

Besides sensitivity, atlases also require tissue areas large enough to capture biological context and analytical flexibility to interpret what is found. Four capabilities of the MERSCOPE Ultra Platform combine to produce atlas-grade data:

Three cm² imaging area. Larger sections, multi-region samples, and cohort-scale studies without registration artifacts or sampling bias.

MERFISH 2.0 sensitivity. MERFISH 2.0 ensures rare populations and rare transcripts are accurately resolved.



Tissue clearing. Many informative atlasing tissues, liver, brain, dense tumor samples, are optically challenging. Clearing reduces autofluorescence and scattering, preserving single-molecule signal across the full section thickness.

Customizable segmentation and analysis. MERSCOPE's pipeline lets researchers tune cell boundary detection and adapt clustering to the biology.

Getting to MERFISH 2.0 quickly

MERSCOPE Pre-designed Panels with Add-on capabilities give researchers a direct path: Existing instruments remain compatible, and labs can apply the enhanced chemistry to projects already in progress. More than 20 validated Pre-designed Panels span human biology, oncology, and dedicated mouse studies.

The atlasing moment

The Human Cell Atlas and disease-focused atlasing efforts are moving from pilot to production scale, and the atlases built now will be cited and expanded on for years. The question is whether a platform finds the cells that matter most: the ones that change everything when you finally see them.

"Cell atlases need more than cell-type identity. Spatial technologies like the MERSCOPE Platform are how we add location and function to that picture, and that context is what makes an atlas useful for understanding tissue biology, not just cataloguing it," said Liat Alyagor, PhD, head of immunohistochemistry, Weizmann Institute of Science.

That is the standard MERSCOPE Ultra was built to meet. ■

regulatory alignment across the field. With initiatives like IAMPS (Industry Alliance for MicroPhysiological Systems), of which MIMETAS is a founding member, industry innovators will work together to advance regulatory acceptance.

The space is evolving quickly, but Vulto emphasized that their focus remains unchanged: building robust human models that help researchers make better decisions.

Improving organoid access

"Organoids are part of a broader innovation focus to help researchers work with more predictive models, more advanced tools, and more connected workflows across the path from discovery to development," commented Heather Hargett, PhD, head of cell biology reagents franchise at **MilliporeSigma**, the U.S. and Canada Life Science business of **Merck KGaA, Darmstadt, Germany**.

The regulatory landscape is becoming increasingly favorable to NAMs. In March 2026, the FDA issued a draft guidance to establish clear validation principles for NAMs, including organoids and *in silico* (or AI) models, when submitted in support of drug applications.

Phasing out animal use for research and regulatory purposes is also supported by the European Commission's *Roadmap Towards Phasing Out Animal Testing for Chemical Safety Assessments*.

HUB's advanced organoid capabilities are now being combined with the company's cell culture expertise, manufacturing scale, global commercial reach, and broad life science portfolio to make organoids a more practical and scalable tool in drug discovery and translational research.

Patient-derived organoids (PDOs) retain individual genetic and phenotypic characteristics, enabling drug response testing across diverse patient backgrounds and disease subtypes. The image shows immunocytochemical (ICC) characterization of human colon PDOs that are positive for the colon-specific marker CA II (*green*), nuclei (*blue*) and actin (*red*). [MilliporeSigma, the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany]

Key priorities include expanding the validated organoid biobank across additional therapeutic areas, tissues, disease states, and patient backgrounds. "Last October, we announced a strategic partnership with Promega Corporation," said Hargett. "By combining our organoid expertise with Promega's advanced reporter technology, we aim to enable high-throughput screening that helps researchers identify safer and more effective drug candidates."

The case of petosemtamab, developed by Merus, is a notable example of the real-world impact of organoid technology. Petosemtamab's efficacy was tested using HUB organoids. The EGFR x LGR5 bispecific antibody has received FDA Breakthrough Therapy Designation for use in combination with pembrolizumab for first-line treatment of PD-L1-positive recurrent/metastatic head and neck squamous cell carcinoma (HNSCC). A global Phase III trial is ongoing. Recently, Genmab acquired Merus for approximately $8 billion USD.

Adopting organoid technology is a capital efficiency strategy, according to Hargett. Patient-derived organoids retain individual genetic and phenotypic characteristics, enabling drug response testing across diverse patient backgrounds and disease subtypes. Organoids support a "fail fast" approach by identifying non-viable candidates earlier, reducing costly late-stage clinical trial failures, and allowing companies to redirect resources toward the most promising programs. GEN

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THE CONFIDENCE GAP:

Why Drug Discovery's **Data Explosion** Hasn't Solved Its **Billion-Dollar Decision** Problem

By Laurence Arnold, PhD

By prioritizing proof over progress, decision-makers can fail faster—and smarter

Laurence Arnold, PhD
Head of R&D
Pelago Bioscience

We've never had more data in drug discovery. Yet despite this explosion in capability, our industry's most fundamental challenge remains stubbornly intact: making confident early decisions about which drug programs deserve billion-dollar investments, and which should be shelved.

It costs two to three billion dollars to bring a drug to market, with a 90% failure rate, often higher. These numbers mask something more troubling. We're not just failing because biology is hard; we're failing because the mountains of data we're generating aren't giving us what we actually need at decision points that matter.

In my view, we don't have a data volume problem—we have a data relevance problem.

Biological activity is not relevance

Traditional drug discovery relies on a "dissect and build" approach: isolate one variable, measure it in a controlled environment, then extrapolate. It's disciplined. It's reproducible. And it has delivered important medicines.

But the persistently high failure rate in drug development tells us we're reaching the limits of this approach. In reality, biology operates through cascading networks, feedback loops, and context-dependent equilibria. These are dynamic biological systems where cause and effect rarely follow straight lines.

We've successfully drugged only about 650 of 20,000 potentially druggable proteins. Not because scientists lack talent, but because for most targets, we don't have robust ways to measure what matters—the initiating molecular event in a biologically relevant context.

We're good at measuring activity. What we struggle with is measuring relevance.

An assay telling you a compound binds to your target protein is useful, but does it bind in living cells? In the disease context that matters? With the pharmacokinetics to reach patients? A compound brilliant in a purified enzyme assay might never reach its target in cells, or it might hit off-targets producing effects through entirely different mechanisms.

The result? Ever-expanding data sets that still don't answer the critical question in modern drug discovery: *Are we making the right decision?*

The cost of borrowed confidence

There's a human dimension here that rarely makes it into industry discussions. Despite what is often repeated in drug discovery circles, scientists in R&D are rewarded for being right, not for being bold.

Most scientists think in terms of "future hindsight": Will we look back and realize we missed something obvious? The responsibility isn't to push programs forward at all costs. It's to execute each step well, knowing that most will fail. Success stories often appear bold in retrospect. In practice, they are usually built on careful, incremental decisions that gradually improve the odds.

So, teams do their jobs with discipline and rigor. They hit milestones, generate data, and advance programs. Everyone knows 90% of projects will fail, but this one has shown activity in the assay, has a plausible mechanism, and has momentum. The data might not be perfect, but it's good enough to keep going.

Until it isn't. And the failure comes late, after years of effort and hundreds of millions spent.

Of course, failure is how science advances. But many of these failures were avoidable earlier. Hard-working teams just didn't have data that would let them make the call with confidence when it mattered most, before massive resources were committed.

What decision-ready evidence looks like

The best experiment isn't always the one that moves your program forward—it's the one that tells you when to stop.

Think of it as taking a stepladder to look over a thick hedge rather than hacking through it with an axe. You might not learn everything about what's inside it, but you'll know much faster whether there's anything worth pursuing on the other side.

The pharmaceutical industry has been built on a model of going through the hedge, but the resource cost and timelines are increasingly untenable. So, what would an alternative, evidence-driven discovery model look like?

Evidence-driven discovery requires a hierarchy of questions. Before optimizing potency or selectivity, can you prove that engaging this target in this context produces therapeutically relevant effects? Not in an abstract system, but in actual disease biology.

This is about front-loading proof of concept before investing in optimization. Measure the initiating molecular interaction early, free from tags or unnatural expression control, in cells and tissues that approximate disease.

It also requires new frameworks for proof of target engagement. We're seeing this with technologies that measure binding in native cellular contexts, patient-derived models, and translational designs that test hypotheses much earlier in preclinical development. The goal isn't replacing traditional assays, but knowing which programs deserve that investment.

Ultimately, the win comes from making the right decision at each stage, even when that decision is to stop.

The path forward

Successful programs will establish coherent lines of evidence from initial target engagement through preclinical models to human proof of concept—and they will do it fast enough to fail early when evidence doesn't align.

This means rigorously testing hypotheses in the real biological context of disease before perfecting molecules or committing billions of dollars.

Some will argue this is unrealistic—that you need optimized compounds, and that shortcuts lead to false negatives killing promising programs. These concerns aren't wrong; they're just insufficient when the old model demonstrably isn't working.

The real question is whether the risk of earlier translational testing exceeds spending nine years and a billion dollars on a target that was never going to work.

Making the call with confidence

Here's what I tell my team: Your job isn't to get a drug to the clinic. Your job is to do each step exceptionally well, building evidence you can defend. Because if we're systematic about gathering the right evidence early, and if we're honest about what the data is—and isn't—telling us, the statistics start working in our favor.

The industry is moving toward evidence-first approaches—technologies validating targets in relevant contexts, translational frameworks testing hypotheses earlier, and computational tools trained on quality data.

But all this data is just noise until it answers the question keeping many of us up at night: *Can I make this call with confidence, or am I crossing my fingers and hoping?*

We won't solve the 90% failure rate entirely. Biology is too complex. But we can close the confidence gap by using the right data, at the right time, to answer the key question: *Should we keep going?*

And sometimes—often, even—the most valuable answer will be *no*. GEN

Laurence Arnold, PhD, is the head of R&D at Pelago Bioscience.

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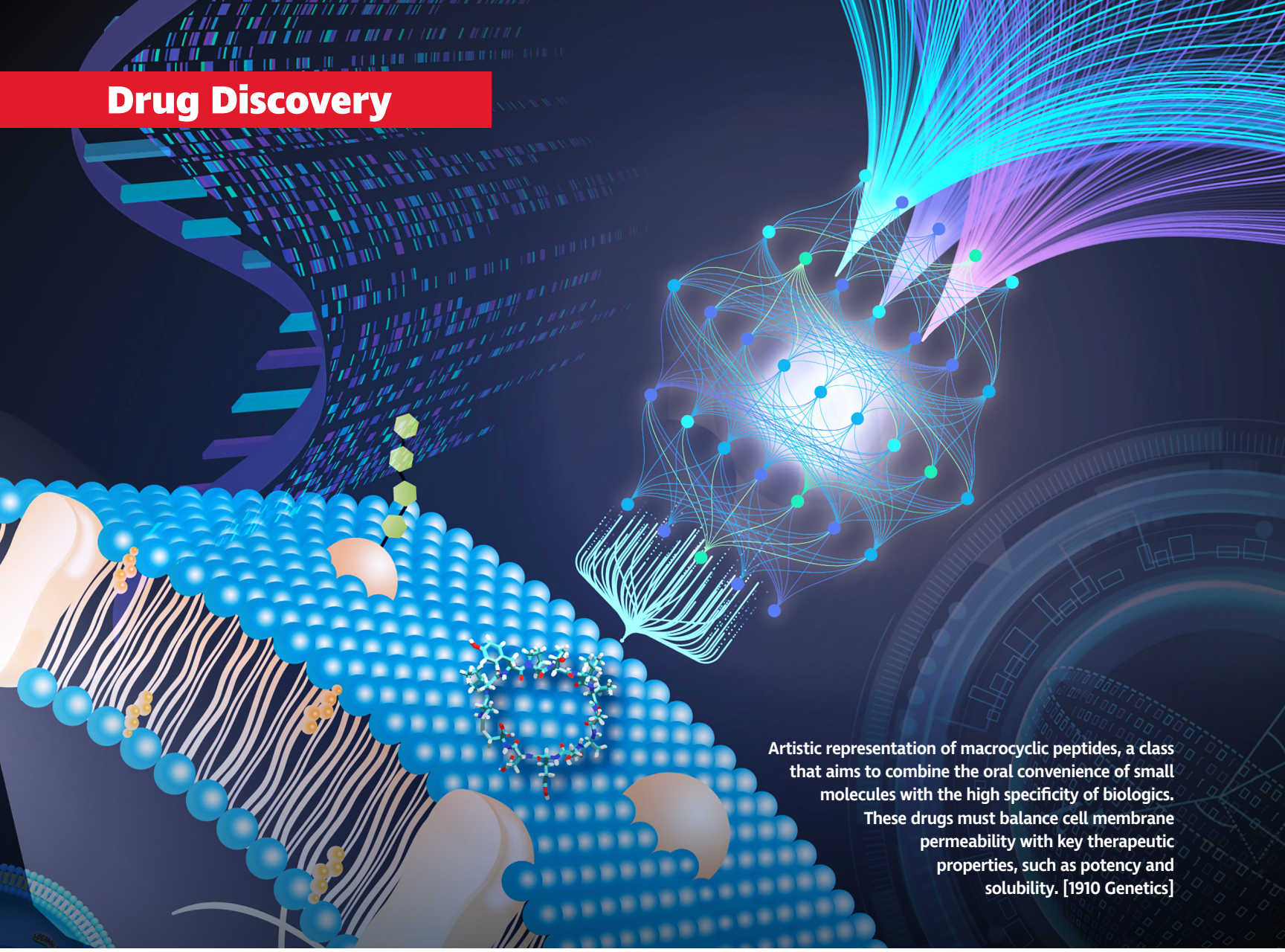


Artistic representation of macrocyclic peptides, a class that aims to combine the oral convenience of small molecules with the high specificity of biologics. These drugs must balance cell membrane permeability with key therapeutic properties, such as potency and solubility. [1910 Genetics]

Novel Therapeutic Modalities

Target the Undruggable

By Fay Lin, PhD

Macrocycles, *de novo* antibodies, and mRNA therapies are expanding the drug discovery toolbox for unmet patient needs

From small molecules and protein therapeutics to gene therapies, biotech industry players have placed their bets on a wide range of modalities that push the limits of what was once considered "druggable."

AI biologics company, **Absci**, focuses on rational antibody design to bypass labor-intensive experimental screens. The ability to computationally design antibodies from scratch, or *de novo*, without reference to a known binder, could transform an antibody drug market projected to reach $445 billion within the next five years.

Unveiled in January, the company's latest protein design model, Origin-1, generated developability-optimized antibodies that achieved nanomolar binding affinity and functional inhibition of IL36RA, a therapeutic target for squamous cell carcinomas. By simulating the delivery of pro-inflammatory cytokine, IL-36, the AI-designed drug candidate boosts intratumor immune response for cancer control.

Origin-1 generates *de novo* antibodies for "zero-prior" epitopes, or target sites that lack structural data from known protein-protein complexes. Sean McClain, CEO of Absci, emphasizes the approach as a "more expansive" version of *de novo* design that requires only a monomeric structure as input to generate viable candidates.

Nathaniel Bennett, PhD, co-founder at **Xaira Therapeutics**, highlights that Absci's atomic-level experimental validation contributes to the field's understanding of how AI will play a major role in therapeutic development, particularly for expanding the range of tractable drug targets.

"This is a solid piece of work that shows how AI-driven antibody design continues to mature," says Bennett, "particularly in settings with limited prior structural information."

Janani Iyer, PhD, head of AI/ML product at Absci, emphasizes that the targets that most often strike interest from pharma partners are typically less studied and lack epitope structure in the public domain. "We're focused on building an AI platform technology that unlocks really unmet needs," she said.

Permanently bound

While highly precise therapeutics, biologics, such as antibodies, are typically constrained to intravenous delivery. A growing number of biotech companies are expanding the capabilities of small molecules, which offer the advantage of convenient oral administration.

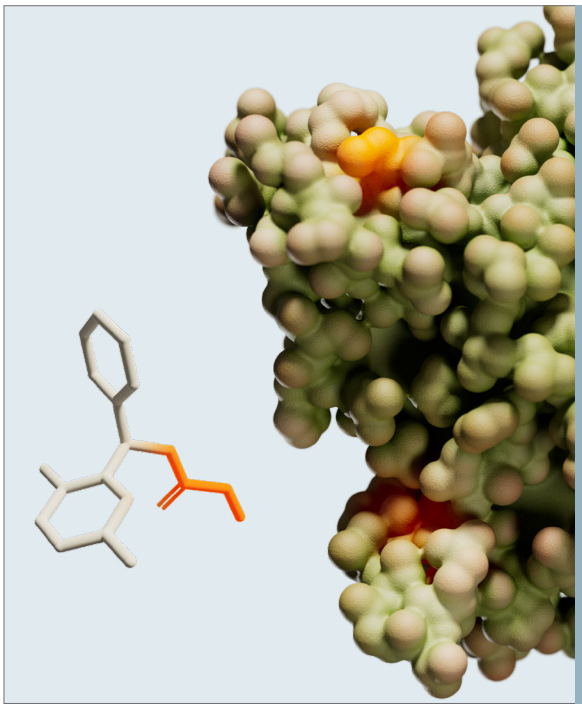
Unveiled from stealth last October, **Expedition Medicines** leverages generative AI to design small-molecule drugs that target shallow pockets using covalent chemistry. The Flagship Pioneering spinout targets a range of traditionally undruggable sensors, regulators, and transcription factors, where disease is driven by interactions across protein surfaces. These small molecules remain inert inside the body until activated by the appropriate protein catalyst.

"Small molecules have historically been more challenging for generative AI, but I think we are at an inflection point, with the right chemistry insights, data, algorithms, and compute finally coming together," said Molly Gibson, PhD, CEO of Expedition.

She notes that Expedition's technology contrasts with many of today's molecular design efforts, which use 3D atomic positions to model reversible interactions in deep pockets.

The company's tech stack trains AI models on high-throughput mass spectrometry data that measures the potency of each small molecule against 20,000 sites in the proteome. These fit-for-purpose datasets are advantageous over DNA-encoded libraries (DELs), which are burdened by substantial noise that can limit predictive power.

Expedition is focusing on demonstrating clinical proof points. In a partnership with **Pfizer**, the startup is identifying target molecules correlated with prostate cancer disease progression and treatment resistance. As a long-term goal, the team plans to expand the proteomics platform to additional modali-



Expedition Medicines leverages generative AI to design small-molecule drugs that hit shallow pockets using covalent chemistry. The approach targets a wealth of traditionally undruggable sensors, regulators, and transcription factors, where interactions across surfaces drive disease. [Expedition Medicines]

ties, such as proximity events that drive protein degradation or stability.

Biologic in a pill

AI drug developer, **1910 Genetics**, has recently tackled macrocyclic peptides, a class that aims to combine the oral convenience of small molecules with the high specificity of biologics. Historically, these compounds have struggled to balance cell-membrane permeability with key therapeutic properties such as potency and solubility.

To address this gap, 1910's AI model, PEGASUS, is trained on a multi-modal dataset that generates billions of cyclic peptides separated by permeability-related characteristics and solvent-dependent computational simulations. PEGASUS was able to demonstrate the first cyclic peptides with more than two polar or ionizable fragments to achieve *in vitro* cell-membrane permeability.

Jen Asher, PhD, founder and CEO of 1910, describes the model as a "versatile tool" that accelerates the design-make-test cycle by triaging compounds for synthesis, supporting lead optimization, and designing new starting peptides with desired properties.

With a company name that references the year that the first patient was diagnosed with sickle cell disease in the United States, the first condition for which the field identified a molecular basis, 1910 is committed to multi-modality drug discovery. The company's platform also houses CANDID-CNS, an AI model that predicts small molecule blood-brain barrier (BBB) penetration within Beyond-Rule-of-5 (bRo5) chemical space to advance therapies for neurological disease.

With only about two percent of small-molecule drugs able to cross the BBB, accurate penetration prediction can identify promising candidates that are more likely to succeed in the clinic. The model achieved an 87% success rate for predicting bRo5 small molecule brain penetration and distribution, outperforming a 56% success rate for the industry standard, Pfizer's CNS Multiparameter Optimization (CNS-MPO) score.

Encrypted message

Jacob Becraft, PhD, CEO at **Strand Therapeutics**, is placing his bet on programmable mRNA therapeutics for cancers and autoimmune diseases. Strand is among a vibrant genetic medicine ecosystem, where engineered vehicles, such as adeno-associated vectors (AAVs) and lipid nanoparticles (LNPs), deliver therapeutic genetic material into patient cells to produce therapeutic proteins. These medicines must achieve therapeutic potency in the right tissues while avoiding off-target effects. Yet, targeted delivery beyond the liver remains a challenge.

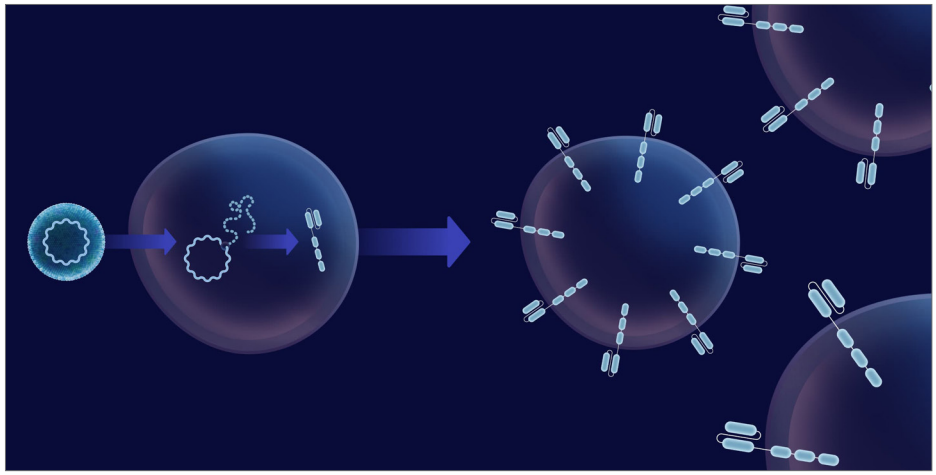
Strand's technology addresses this gap by enabling selective mRNA expression within cancer cells while sparing healthy tissue. This approach allows mRNA to be delivered broadly while targeting expression to the intended tumor cells.

"It's like an encrypted message. It doesn't matter who picks up my message because they can't read it," Becraft said. "If the protein doesn't get created, then it's not off-target." The tech stack challenges the "old school mentality" that mRNA biodistribution is the key metric that defines off-target effects.

Strand's technology leverages a machine learning–driven approach that applies molecular sensors to detect microRNA expression signatures distinguishing tumor cells from healthy cell types. As an example, liver-specific microRNAs bind to target sites in the 3′ UTR of the delivered mRNA to suppress its expression in healthy hepatocytes and prevent off-target effects.

Last May, Strand announced the Phase I dose-escalation trial for STX001, a programmable, self-replicating mRNA therapy designed to treat advanced solid tumors by producing IL-12 directly in the tumor microenvironment. Notably, STX001 demonstrated an abscopal response, in which localized treatment of a single tumor led to a systemic immune response that reduced distant tumor sites. The company looks to advance the candidate to Phase II trials.

As the therapeutic toolbox continues to expand, the field is working to close the "undruggable" gap. GEN



STX-005 extends the same programmable mRNA platform behind STX-001 to *in vivo* CAR T therapy, using circular RNA and targeted systemic delivery to generate CAR T cells directly inside the body. The approach is designed to produce long-term, cell-specific expression without the *ex vivo* manufacturing required by conventional CAR T. The program extends the company's work in targeted, safe, and effective systemic delivery and has potential applications to autoimmune diseases and blood cancers. [Strand Therapeutics]

ProPure™ Endotoxin-Free Proteins for Reliable Cancer Research

Minimize immune interference in sensitive oncology applications

In cancer research and therapy development, even trace levels of endotoxins (LPS) in recombinant proteins can severely distort results. In discovery and preclinical studies, endotoxins are silent disruptors of animal immunization, sensitive biological assays, and toxicity assessments, compromising results and safety evaluations. Endotoxin-free recombinant proteins are therefore essential for generating reliable research data and successful development of next-generation cancer therapeutics.

Invisible interference in cancer therapy and vaccine development

Endotoxin contamination can severely compromise antibody generation in animal models. Even small amounts of endotoxins can alter the host's immune response, reducing antibody specificity, consistency, and overall quality. Endotoxin-contaminated recombinant proteins can subtly—but significantly—alter cellular behavior through immunostimulatory and cytotoxic effects. Endotoxin-induced systemic inflammation in animals can further disrupt experiments, potentially leading to study suspension or even termination.

In cell-based studies, endotoxin contamination can be a hidden disruptor. Immune cells such as dendritic cells, macrophages, monocytes, and T cells can respond strongly even to trace amounts of endotoxins, leading to cytokine release, altered proliferation, or unexpected activation. These effects can easily produce misleading or non-reproducible results.

The demand for endotoxin-free reagents is even more critical in the development of cancer vaccines. Since these therapies rely on precise modulation of the immune system, endotoxin contamination can trigger unintended immune activation, masking the true efficacy of the vaccine candidate and introducing safety risks. Using endotoxin-free proteins is therefore vital to accurately evaluate immunogenicity and support safe clinical translation.

Sino Biological's ProPure™ solution to minimize endotoxin risk

While pharmacopeial guidelines such as USP <85> provide general limits for endotoxin, cutting-edge immunology and translational oncology studies often require far stricter control. Sino Biological's ProPure endotoxin-free recombinant proteins are designed to eliminate this variable at the source, supporting reliable results from early discovery through IND-enabling studies. Produced at the state-of-the-art Center for Bioprocessing (C4B) in Houston, Texas, ProPure reagents are rigorously controlled to achieve levels as low as 0.05 EU/mg, with select products reaching an exceptional 0.01 EU/mg—over ten times lower than typical industry standards.

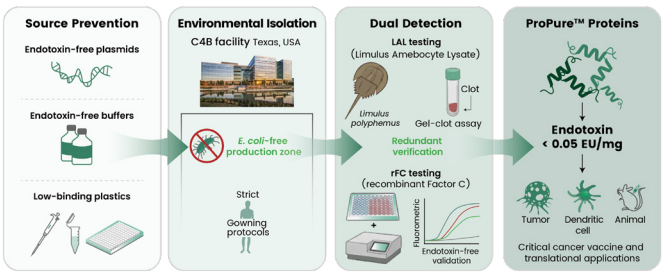
By incorporating endotoxin-free proteins, researchers in cancer therapy and vaccine development can confidently achieve consistent and accurate results in critical applications, including:

- Animal immunization for antibody generation—ensuring high-quality antibodies and predictable host immune responses.
- Preclinical toxicology and pharmacokinetics (PK)—minimizing confounding immune activation in animal models.
- *In vitro* cell proliferation and differentiation assays—reducing false positives caused by endotoxin-sensitive cells such as dendritic cells, macrophages, and T cells.
- Precise detection and quantification of cytokines—supporting reliable immunological readouts and biomarker analyses.

How ProPure achieves ultra-low endotoxin levels

ProPure quality is not achieved by end-stage cleanup alone. C4B employs an integrated Prevention–Isolation–Detection strategy across the entire production lifecycle, ensuring that ProPure proteins arrive ready for use in the most demanding oncology and immunology applications.

- Prevention at the source: Endotoxin-free plasmids and buffers, low endotoxin-binding plastics, and stringent clean-in-place (CIP) procedures minimize endotoxin introduction from cloning through purification.
- Environmental isolation: The facility follows an *E. coli*-free principle, eliminating a major source of endotoxin introduction in recombinant protein production.
- Dual detection: Each batch is tested using Limulus Amebocyte Lysate (LAL) and/or recombinant Factor C (rFC) assays for sensitive, redundant detection, and fully traceable batch data.



ProPure triple-control strategy for ultra-low endotoxin.

With advanced technologies and rigorous quality control, Sino Biological delivers endotoxin-free proteins that meet the needs of highly sensitive research and translational applications. ProPure proteins help researchers reduce variability, improve reproducibility, and accelerate the development of next-generation cancer therapies. ■

Learn more about ProPure™ endotoxin-free proteins at sinobiological.com/category/endotoxin-free-proteins

Sino Biological

The discovery of most—nearly all—drugs depends on mass spectrometry (MS) in some way. The ongoing advances in this technology allow even more ways to use MS in the search for more and better treatments. [Patamaporn Umnahanant/ Getty Images]

Mass Spectrometry's Discovery Revolution

By Mike May

Next-generation MS platforms are transforming drug discovery by revealing complex biology earlier, faster, and at unprecedented depth

Mass spectrometry (MS) has quietly undergone one of the most consequential evolutions in modern drug discovery. Once viewed primarily as a confirmatory analytical tool, it is now reshaping how researchers identify, validate, and optimize therapeutic candidates. Across chemoproteomics, metabolomics, immunopeptidomics, and beyond, MS is increasingly positioned not at the end of the pipeline—but at its beginning, where the most crucial decisions are made.

"Mass spectrometry is no longer just a downstream analytical checkpoint," says Aaron Robitaille, PhD, the senior director of product & vertical marketing of mass spectrometry at **Thermo Fisher Scientific**. "It is increasingly serving as a discovery engine."

This shift reflects a broader transformation across the pharmaceutical industry: from hypothesis-driven experimentation toward data-rich, systems-level interrogation of biology.

Seeing biology more clearly

Drug discovery has always struggled with a fundamental problem: Biology is complex, noisy, and often opaque. Many of the molecules that determine therapeutic success are low in abundance, transient, or entirely unknown. MS addresses this challenge by enabling researchers to observe biological systems with unprecedented depth and specificity.

According to Robitaille, MS now supports nearly every stage of early discovery—from target identification and engagement to pharmacokinetics and mechanism-of-action studies. One of its most transformative applications is chemoproteomics, where researchers can directly measure drug-protein interactions within living cells. This enables scientists to evaluate not just whether a compound binds its intended target, but also whether it interacts with unintended ones.

Crucially, MS is moving upstream in the discovery pipeline. "What makes that important is not merely breadth. It is timing," Robitaille notes. By enabling high-throughput screening with detailed molecular readouts, MS helps eliminate poor candidates earlier—saving time, cost, and effort.

Technological advances are driving this shift. Historically, researchers faced trade-offs between speed and sensitivity, or between targeted and untargeted analyses. Newer platforms are collapsing these compromises. Hybrid acquisition methods, for example, allow targeted and untargeted data to be collected simultaneously in a single experiment, enabling both hypothesis testing and discovery.

The Thermo Scientific Orbitrap Astral Zoom MS exemplifies this convergence. Built around parallelized acquisition and enhanced ion handling, the system delivers high throughput, deep proteome coverage, and precise quantitation—all in one platform. Its ability to process hundreds of samples per day while quantifying thousands of proteins illustrates how MS is becoming both scalable and decision-ready.

Interrogating biology at scale

For Mike Knierman, biopharma workflow manager at **Agilent**, the expanding role of MS reflects the growing complexity of new therapies. "Drug discovery today spans multiple therapeutic modalities, including small molecules, monoclonal antibodies, oligonucleotides, and cell-based therapies," he explains. MS provides a unifying analytical backbone across this diversity.

One of the most significant recent developments, Knierman emphasizes, is MS's ability to interrogate biology at scale. Techniques such as proteomics, metabolomics (*See Sidebar*), and lipidomics allow researchers to observe how candidate drugs perturb entire cellular systems, rather than isolated targets. This systems-level insight is essential for understanding the mechanism of action and identifying off-target effects early in development.

Emerging measurements—such as protein turnover—are also enabling new therapeutic strategies. These include targeted protein degradation approaches, which require a detailed understanding of dynamic protein lifecycles rather than static abundance.

Agilent's Revident LC/Q-TOF platform reflects this trend toward intelligent, high-resolution analysis. Designed for accurate-mass performance with built-in diagnostics, the system incorporates features that automate quality control and maintain data consistency. Its ultra-fast detector supports a wide dynamic range without sacrificing resolution, enabling confident identification and quantitation in complex biological samples.

Equally important are workflow innovations. The platform's Intelligent Reflex capabilities automate routine checks—such as calibration verification and carryover detection—reducing manual intervention and ensuring consistent performance. In drug discovery environments where throughput and reproducibility are crucial, these features help maintain data integrity while accelerating timelines.

Ultimately, Knierman highlights MS as a driver of "biology-driven discovery," where decisions are guided by comprehensive molecular data rather than limited readouts.

A shift in discovery models

Todd Stawicki, senior global market development manager for pharma, **SCIEX**, places MS within a broader transformation of drug discovery itself. The industry is moving away from traditional *in vivo* models toward more complex *in vitro* systems—such as organoids and tissue-based assays—in an effort to reduce impacts to laboratory animals and rising global regulatory efforts.

This shift dramatically increases the number and complexity of experimental endpoints. "Many or most of these endpoints are best served by mass spectrometry," Stawicki notes. As a result, MS is becoming indispensable for analyzing the rich datasets generated by these models.

MS is also deeply embedded throughout the discovery lifecycle. In the early stages, it supports proteomics and complements genomic studies. It plays a central role in hit identification and lead optimization, and remains crucial in ADME (absorption, distribution, metabolism, and excretion) and DMPK (drug metabolism and pharmacokinetics) studies.

Technological innovation continues to expand MS's capabilities. Acoustic ejection-based MS, for example, enables rapid, label-free screening, while advanced systems—like the SCIEX 7500+ system—address one of the field's most persistent challenges: balancing sensitivity with dynamic range.

As new drug modalities become more potent and targeted, they often exist at extremely low concentrations in complex biological matrices. This creates a dual requirement for high sensitivity and a broad quantitation range. The SCIEX 7500+ system meets this need, enabling accurate measurement across diverse tissues and concentration levels.

Robustness is another key consideration. SCIEX Mass Guard technology, for instance, enhances system uptime, ensuring that high-throughput workflows can run reliably over extended periods. In an environment where delays can be costly, this operational stability is as important as analytical performance.

Balancing throughput and insight

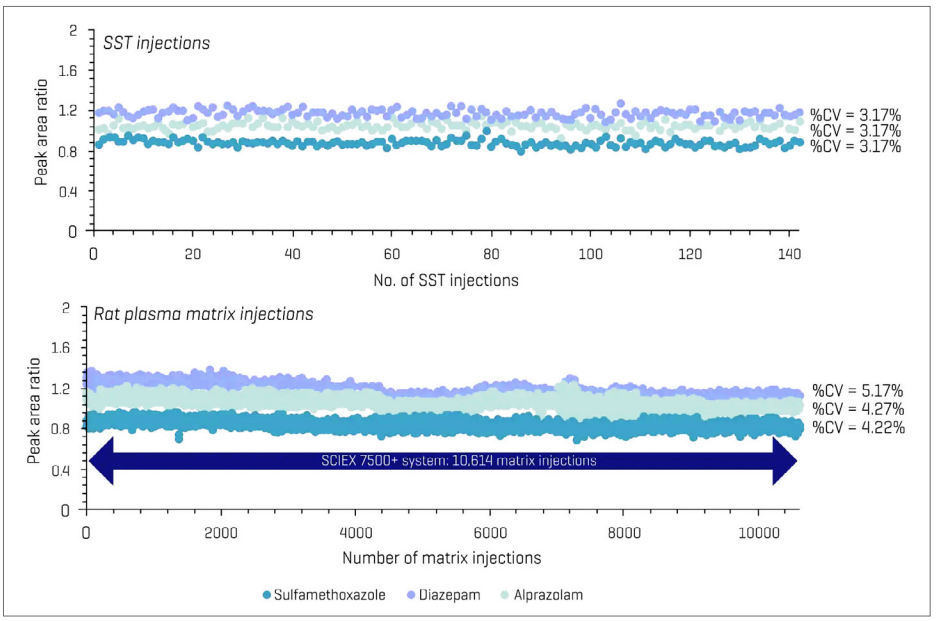
Shimadzu's perspective underscores the importance of versatility in modern MS workflows. "Mass spectrometry has become one of the most versatile analytical tools in drug discovery," says Lihini Mendis, PhD, LCMS product specialist at Shimadzu Scientific Instruments, noting that it now supports everything from early screening to preclinical development.

A major recent trend is the push toward higher throughput without compromising data quality. Rapid LC-MS methods and triple quadrupole systems are increasingly used to process large sample volumes efficiently, particularly in quantitative workflows such as bioanalysis and DMPK studies.

At the same time, qualitative MS capabilities are expanding. High-resolution instruments, combined with advanced fragmentation techniques, allow researchers to gain deeper structural insights into complex molecules such as lipids and metabolites. This dual capability—quantitative precision and qualitative depth—enables scientists to answer both "how much" and "what exactly" within the same experiment, Mendis explains.

Shimadzu's portfolio reflects this balance. Single-quadrupole systems provide accessible, high-throughput screening, while triple-quadrupole platforms emphasize stability and reproducibility for quantitative analysis. High-resolution instruments extend capabilities into accurate-mass analysis and structural elucidation, all while maintaining user-friendly operation.

The overarching goal is not complexity for its own sake, but meaningful data that supports confident decision-making. By focusing on workflow efficiency and reliability, Shimadzu aims to streamline the path from data acquisition to actionable insight.



Analysis of a system suitability test (SST, top) and rat plasma matrix (bottom) injections on the SCIEX 7500+ system for three drug compounds shows coefficients of variation (%CV) of three to five percent across more than 10,000 injections of rat plasma. [SCIEX]

A proteoform-centric vision

While incremental improvements in speed and sensitivity have driven much of MS innovation, **Bruker's** recently introduced timsOmni system points toward a more fundamental shift: a move toward protein-centric analysis at the level of intact proteoforms—structurally distinct variants of proteins that arise from genetic mutations, alternative splicing, or post-translational modifications.

The platform introduces a multimodal trapping approach that enables precise control over ion reactions, supporting a wide range of fragmentation techniques. This flexibility allows researchers to tailor experiments to extract detailed structural information from complex biomolecules.

Rather than focusing solely on peptides

Measuring Direct, Bystander, and Off-Target ADC Killing with the HiBiT TCK Platform

Promega's nonlytic, bioluminescent bioassay platform that distinguishes bystander from direct cytotoxicity in a single co-culture experiment

The efficacy of biologic-based immunotherapies relies on their ability to induce apoptosis and cell death through the recruitment and activation of immune effector cells. Biologic-based immunotherapies come in a variety of formats, such as antibody drug conjugates (ADCs), chimeric antigen receptor (CAR) T cell therapy, and monoclonal antibodies (mAbs), to name a few. For payload-linked formats like ADCs, one challenge is verifying delivery of the cytotoxic payloads to only targeted cells in a heterogeneous tumor environment.

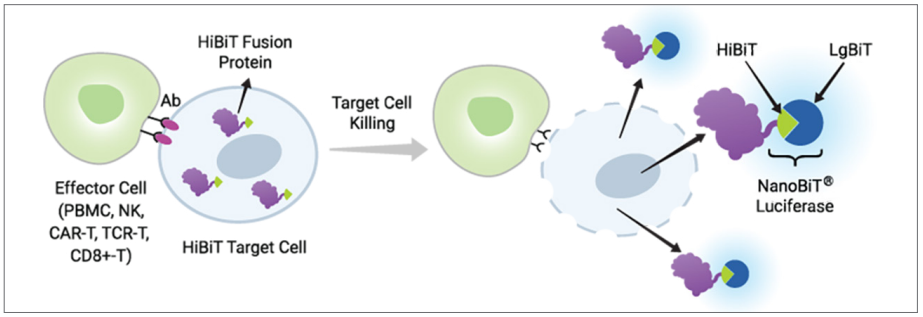
To help address this challenge, Promega's HiBiT Target Cell Killing (TCK) platform is a streamlined, bioluminescent cell-based system that measures cytotoxicity with specificity, simplicity, and sensitivity during therapeutic development. The platform supports all major cell-killing paradigms, including CAR-T cell-mediated killing, antibody-dependent cellular cytotoxicity (ADCC), T cell-dependent cellular cytotoxicity (TDCC), antibody-dependent cellular phagocytosis (ADCP), and ADC bystander killing.

How HiBiT TCK works

Target cells are engineered to express a HiBiT fusion protein that remains intracellular until cell death. Upon membrane disruption, HiBiT is released into the medium, where it binds cell-impermeable LgBiT to form functional NanoBiT® luciferase. The luminescent signal is proportional to target cell death alone, with no contribution from effector cells, making the platform ideal for co-culture experiments. The workflow requires no washing, loading, or staining steps and produces robust signal-to-noise with as few as 2,000 target cells per well.

A growing library of thaw-and-use, functionally tested cell lines addresses blood cancer targets, including B cell lymphoma and leukemia, myeloid leukemia, and multiple myeloma (Raji, Ramos, H929), as well as solid tumor targets for ovarian carcinoma, breast adenocarcinoma, and lung carcinoma (SKOV3, SK-BR-3, OVCAR3). HiBiT-containing target cell lines can also be custom tailored.

ADCs deliver cytotoxic payloads to antigen-expressing tumor cells, but tumors are antigenically heterogeneous. When an ADC's payload is released inside a targeted cell, it can diffuse and kill neighboring antigen-negative cells. This bystander killing can extend therapeutic coverage across a mixed tumor, or it can damage healthy adjacent tissue. The outcome depends largely on linker-payload chemistry: Cell-permeable, cleavable payloads produce high bystander activity, while cell-impermeable payloads do not. Characterizing this activity during development is essential but difficult with conventional cytotoxicity assays, which cannot attribute cell death to specific populations in a co-culture.



Promega

Principle of the HiBiT TCK Bioassay. Cytotoxic mAbs and/or effector cells are incubated with target cells expressing a HiBiT fusion protein. Upon killing of the target cell, the HiBiT fusion protein is released and binds extracellular LgBiT to create a functional NanoBiT® Luciferase enzyme. Luminescence is measured using a luciferase substrate and the GloMax® Discover System.

ADC bystander testing

The Bystander Killing Assay uses a three-cell-line design: wild-type target cells (HiBiT) to measure direct ADC cytotoxicity, wild-type target cells ("Dark", no HiBiT) to serve as the antigen-expressing bystander driver, and antigen-KO cells (HiBiT) to specifically measure bystander killing. In the assay, ADC binds the "Dark" antigen-positive cell and the payload is internalized. If the released payload diffuses and kills neighboring antigen-KO HiBiT cells, the resulting luminescence is specific to bystander killing. Because HiBiT remains intracellular until membrane disruption, only dead target cells contribute signal. Effector or bystander driver cells do not.

Proof of concept

To demonstrate proof of concept, the HiBiT TCK bioassay was used on SKOV3 cells with two approved HER2-targeting ADCs, disitamab vedotin with a cleavable MMAE payload and ado-trastuzumab emtansine with a non-cleavable DM1 payload. The assay confirmed positive bystander killing with disitamab vedotin. Conversely, Kadcyla demonstrated a negative bystander killing effect. CellTiter-Glo™, which reports total well viability without distinguishing cell populations, was unable to make this distinction, demonstrating the power of the HiBiT TCK Bioassay. The same principle was validated with loncastuximab tesirine on Raji/CD19-KO co-cultures.

The examples validate that the streamlined HiBiT TCK platform measures cytotoxicity with specificity, simplicity, and sensitivity. Since the resulting luminescent signal is specific to the engineered target cell, the bioassay is well-suited for mixed co-culture experiments during development efforts. Beyond bystander applications, the HiBiT TCK platform supports ADCC with PBMC effectors, TDCC with CD8+ T cells, and CAR-T killing assays across a 4–72 hour time course. ■

or simplified representations of proteins, the system emphasizes intact protein analysis. This is particularly important for identifying proteoforms. These variants often play critical roles in disease but are difficult to detect using conventional approaches.

The timsOmni platform enables detailed mapping of such variations, including modifications, such as acetylation and glycosylation, that influence protein function and cellular signaling. By combining high sensitivity with advanced fragmentation methods, it allows researchers to generate comprehensive sequence information and localize modifications with precision.

Importantly, this capability extends beyond discovery into biopharma development and quality control. The ability to characterize therapeutic antibodies and other biologics at the proteoform level has significant implications for both efficacy and safety.

Supporting software further enhances this capability by translating complex spectral data into actionable insights. Advanced algorithms enable *de novo* sequencing, charge state assignment, and modification identification, making it easier for researchers to navigate the complexity of proteoform analysis.

Triple-quadrupole MS systems can be used in drug discovery for bioanalysis and studies of drug metabolism and pharmacokinetics. [Shimadzu Scientific Instruments]

Accelerating insights

As therapeutic modalities become more complex, the need for faster, more precise characterization tools has never been greater. David Curtin, vice president and general manager, biologics business, Waters Analytical Sciences, **Waters Corporation**, highlights how emerging platforms are enabling researchers to generate deeper insights earlier in the development cycle—when those insights can have the greatest impact.

As one example, Curtin describes the Xevo CDMS platform as a breakthrough in capability and accessibility. As the first dedicated benchtop charge-detection mass spectrometry system, it enables measurement across a wide spectrum of mega-mass biomolecules. Crucially, it supports "characterization in process development when decisions matter most," Curtin says, allowing teams to act on high-quality data in real time.

Speed is one of its most transformative advantages. "Xevo CDMS delivers accurate analysis in less than 10 minutes," Curtin explains. This represents a dramatic improvement over traditional workflows that could take hours, days, or even weeks when outsourced. The result is a shift to same-day decision-making, fundamentally changing how process development is executed and optimized.

Multiomics Mass Spec Workflows in Drug Discovery

Advances in end-to-end multiomics platforms and the underlying scientific knowledge now enable faster and more precise biomarker discovery, mechanistic insight generation, and therapeutic design—core drivers of modern drug discovery programs. Within this integrated ecosystem, mass spectrometry-based metabolomics serves as a central analytical modality, offering the ability to quantify large numbers of metabolites from a single sample with high sensitivity and rapid turnaround.

Metabolomics supports biochemical pathway-level interpretation, where a primary biomarker can be contextualized alongside upstream and downstream metabolites to inform target identification, pathway modulation, and pharmacodynamic response assessment. Rather than focusing solely on the discovery of novel metabolites, emerging approaches emphasize the identification of characteristic metabolic signatures that differentiate disease states, therapeutic responses, or mechanistic subtypes.

Realizing this potential requires the development and deployment of AI enabled data analysis workflows that can reduce interpretation time, expand the breadth of detectable targets, and uncover complex patterns of metabolite perturbation. These capabilities ultimately enhance the precision and effectiveness of targeted therapeutic development.

***—Taraka Donti, PhD, director of lab services at* Revvity Omics**

Efficiency is another key differentiator. Curtin notes that "the system requires up to 100 times less sample than current methods," addressing a long-standing limitation in biopharma research. With reduced sample demands, scientists can run more experiments per batch, leading to "lower cost, higher yields, fewer impurities, and faster time to market," he says.

Beyond operational improvements, the platform unlocks new scientific possibilities. Curtin emphasizes that it delivers direct mass and charge measurements for individual 100-kilodalton to 150-megadalton molecules, including complex structures such as glycosylated proteins, viral vectors like AAV, and lipid nanoparticles. In many of these cases, "CDMS isn't just a better option; it's the only option," Curtin says.

Ultimately, Curtin underscores the broader impact: researchers are now generating "fast, accurate orthogonal data" that validates existing approaches while opening entirely new lines of inquiry. Scientists, he says, are "asking and answering questions they couldn't tackle before"—a powerful indicator of how this technology is advancing the development of therapies for diseases including cancer, heart disease, and Alzheimer's.

From data to decisions

Across all these perspectives, a common theme emerges: MS is no longer defined by its ability to generate data, but by its ability to inform decisions. This clarity is transforming drug discovery. By revealing off-target effects, validating mechanisms of action, and identifying biomarkers at early stages, MS helps reduce uncertainty and improve success rates. It allows researchers to prioritize the most promising candidates and eliminate those unlikely to succeed.

As Robitaille puts it, the ultimate value of modern MS lies in "the ability to see meaningful biology early enough to act on it." In an industry where time, cost, and complexity are ever-increasing, that capability might prove to be one of the most important advances of all. GEN

Thought Leader

Continued from page 31

not as dire as with heart- and pituitary-derived proteins. Thus, the transition is progressing, but is not as far along.

Keys to producing recombinants

To justify switching to a recombinant protein, the recombinant must perform comparably to the native protein it is intended to replace. Early recombinants did not perform well, resulting in the skepticism seen initially. In antibody-based assays, even subtle structural differences can translate into poor recognition, reduced sensitivity, or altered calibrator performance. Overcoming these issues requires more than simply expressing a protein in a convenient host; it requires a project development and testing strategy tailored to the nuances of IVD assay development.

At Scripps, our intention was to devise and implement a strategy that would produce recombinants suitable for the IVD industry. The process involves appropriate gene, expression vector, and host cell line selection; tagless protein expression; early and extensive testing in antibody-based systems, including clinical analyzers; and a willingness to revisit any or all of these elements if the desired recombinant is not produced.

This development strategy addresses the concern about recombinant protein performance in the IVD industry. When a recombinant biomarker performs well and can be supplied consistently, without relying on the unstable supply framework of donor materials, the recombinant becomes not just an acceptable option, but the preferred one.

Looking ahead

The IVD industry is at an inflection point, bending toward global acceptance of recombinant biomarkers. The constraints on native tissue supply and quality will not ease; in fact, they will likely intensify. Simultaneously, industry expectations surrounding ethical sourcing, supply chain stability, risk mitigation, and long-term cost control will become more stringent. Given this environment, continued reliance on donor materials is difficult to justify and is perhaps foolish.

Recombinant proteins offer a way forward that unites consistent assay performance with sound business judgement. Disconnected from unreliable tissue supply networks, recombinants support sustainable and ethical sourcing practices, providing IVD assay manufacturers with a stable foundation for planning and growth. The experience of recent years—in reproductive biology, cardiology, and thyroid disease in particular—has shown that when recombinants are developed with clinical assay performance in mind, they can match or even exceed the standards set by native proteins.

Our team has seen the industry's view of recombinants evolve from skepticism to necessity. Focusing on tagless expression and rigorous early testing, recombinants can be produced not as lesser-quality replacements, but as robust solutions. As assay developers and IVD executives look ahead to the next decade of innovation, recombinants are no longer a speculative option. They are the most responsible path toward assuring the continued availability of the tests that patients and clinicians rely on daily. ■

Enhancing Quality and Accelerating the Development of Bispecific Antibodies

By Sherry Gu, PhD

The unique ability of bispecific antibodies (BsAbs) to target two molecules and drive synergistic effects has opened new options for refractory cancers and autoimmune diseases, potentially addressing numerous medical unmet needs. With hundreds of BsAb candidates in clinical trials, first-mover advantage is pivotal. Accelerating BsAb development, without sacrificing quality and safety, has become an urgent priority. However, BsAb development is accompanied by inherent complexities that pose substantial barriers.

For example, unlike mAbs, which rely on a single, homogeneous heavy-light chain pair, BsAbs need two distinct heavy and light chains, which randomly form mismatched by-products that complicate purification, increase structural constraints that cause protein degradation, aggregation, or fragmentation, and reduce yields. These challenges translate into longer development timelines, higher manufacturing costs, and greater technical uncertainty.

Analytical control

Effective development mandates an integrative approach blending comprehensive analytical controls, molecular engineering, cell line development (CLD) and manufacturing, and process optimization, as well as project management to ensure fast track development.

Before initiating assay development, critical quality attributes (CQAs) should be identified and prioritized based on the quality target product profile (QTPP), ensuring that analytical methods and control strategies are fit-for-purpose, risk-based, and aligned with clinical and regulatory expectations. A proactive, QTPP-driven approach enables early detection, monitoring, and control of quality-related risks, supporting robust clone selection, process optimization, and consistent product quality from early development to commercial manufacturing.

Against this framework, developing reliable bioassays for BsAbs presents distinct analytical challenges due to the unique designs that reflect their complicated and innovative mechanism of action (MoA), as well as dual targets/epitopes. Mismatched by-products, unassembled chains/half molecules, and high levels of aggregates cannot be completely avoided. Among them, mismatched species frequently occur in forms that are similar to the target proteins in ways that make them

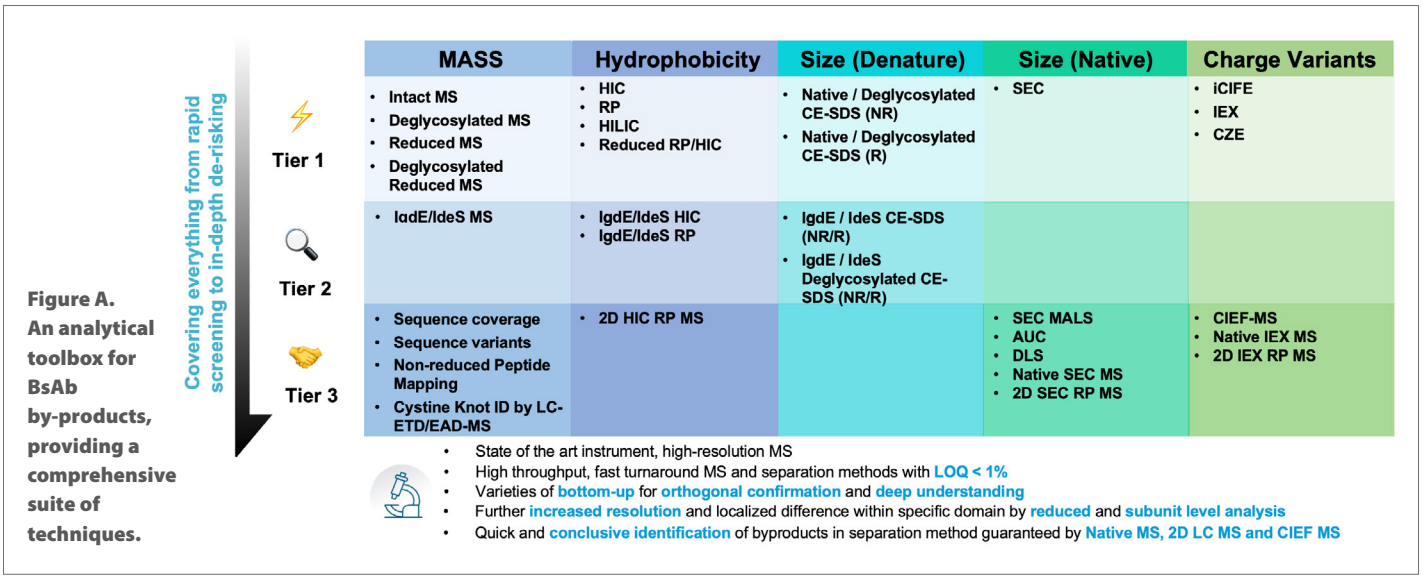


Figure A. An analytical toolbox for BsAb by-products, providing a comprehensive suite of techniques.

indistinguishable by conventional methods.

FDA guidance for BsAb development emphasizes specific considerations for different formats, including aggregates, fragments, homodimers, and other mismatched species, antigen specificity, affinity, avidity, potency, and on/off rates. Phase-appropriate approaches, per regulatory guidance, are widely adopted.

A combination of potency assays is highly preferable to address scientific, medical, and regulatory aspects of biological activities. For example, driven by the MoA, dual binding enzyme-linked immunosorbent assays (ELISAs) that reflect simultaneous binding can be well-developed as robust and QC-friendly release assays in early phases. Characterization bioassays, such as single binding ELISA and binding kinetics by surface plasmon resonance (SPR), can provide a comprehensive understanding of biological activities.

More complex and MoA-reflective cell-based assays can be established as characterization assays in early phases or developed into robust and QC-friendly release assays in later phases.

The existence of mismatched by-product species needs to be experimentally confirmed and evaluated at an early stage. Each existent mismatch species needs to be monitored by appropriate analytical methods to guide clone selection and process development. However, the greatest analytical challenge lies in monitoring mismatched species like heavy chain-heavy chain homodimers and heavy chain-light chain mismatches.

For instance, a four-chain BsAb, composed of two distinct heavy chains and two distinct light chains, could theoretically form nine different four-chain by-products. Among these, the light chain-swapped species could display the same molecular weight and similar physiochemical features as the target molecule, challenging the limits of conventional analytical capabilities such as mass spectrometry (MS).

It is necessary to screen separation mechanisms and select fit-for-use methods that differentiate between target molecules and mismatched by-products, according to the QTPP.

In a case study of an asymmetric four-chain BsAb, intact MS was utilized in the chain ratio study and focused on heavy chain mispairing. When the project entered CLD, a subunit MS method was added to monitor light chain-heavy chain mispairing. At process development, a hydrophobicity interaction chromatography (HIC) method was developed to enable fast testing turnaround. The HIC method was continuously optimized to establish the QL as two percent and became QC ready when the process was locked and ready to move into GMP production.

A powerful analytical toolbox is essential. A smart analytical strategy based on advanced technologies can provide guidance to accelerate process development and realize QTPP-based quality risk management (*Figure A*).

Molecular assembly and stability

Producing high-quality BsAb requires the assembly of stable molecules while avoiding common issues that reduce yields and increase immunogenicity risk, such as chain mispairing and homodimer formation. This involves systematic tuning of key parameters to establish a foundation for successful cell line generation, alongside the development of analytical methods that ensure early detection of CQAs and key by-products.

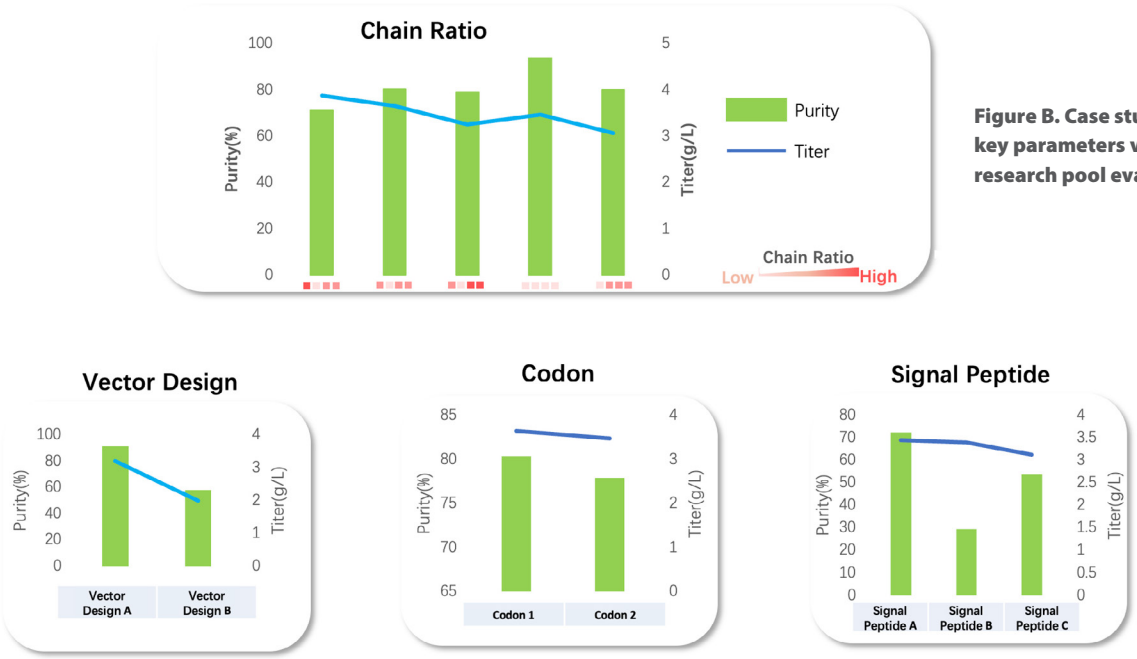


Figure B. Case study: Optimized key parameters via single-round research pool evaluation.

Systematic tuning can be performed in early-stage "research pool" studies. Over a period of about six weeks, these studies use a multi-parametric evaluation framework to select optimal stable transfection conditions.

A case study evaluated the effects of key parameters (vector design, codon usage, signal peptides, chain expression ratios) on product quality and productivity. Such systematic analysis enables the identification of optimal conditions for stable transfection. Meanwhile, the proactive development of suitable analytical methods, such as those described above, ultimately delivers cell lines with optimized performance, while establishing essential quality control measures (*Figure B*).

Building on the foundation established by research pool studies, the choice of host cell platform further boosts the efficiency and stability of BsAb production. For example, the Chinese hamster ovary (CHO) WuXia™ cell line, which has been utilized in the development of over 1,000 cell lines for clinical and commercial manufacturing applications, is extensively used for BsAb.

A new cell line, WuXia TrueSite, leverages site-specific integration technology to rapidly develop stable cell lines with high productivity. It has demonstrated considerable titer improvement and >99% stability, with less than 20% titer reduction after 60 population doubling levels (PDLs). See *Figure C*.

This means that cell line stability is no longer a rate-limiting step for final clone selection, and it may even be possible to eliminate the need for cell line stability studies from the critical path, directly accelerating development timelines. Specifically, WuXia TrueSite enables acceleration of Master Cell Bank (MCB) establishment to 9–10 weeks, cutting the overall conventional development timeline in half.

To date, WuXia TrueSite has been applied to eight BsAb development programs, with an average pool titer of 6.5 g/L (range: 5.8–7.9g/L) and a monomeric purity of at least 90%.

With a robust and high-performing host cell platform secured, supported by optimized cell culture conditions that maximize yield while preserving BsAb stability, integrated bioengineering and cell culture strategies address the intrinsic complexities of BsAb, facilitating efficient transition from clone selection through to downstream processing and manufacturing.

Different BsAb formats necessitate different downstream processes using highly perceptive, tailored approaches. Establishing which processes are suited to which molecules can be a daunting task. However, experience with nearly 200 BsAb projects reveals that some commonalities can be leveraged for greater efficiency.

For example, some BsAbs might share similar engineering strategies or key features such as T cell receptor (TCR) constant domains, single-chain variable fragments (scFv), common light chains, knobs-into-holes (KIH), or charge pairing. Prior experience with common elements can guide tailored downstream strategies that can be tested on new BsAbs with similar designs.

For instance, ScFv typically causes 10–20% aggregates that can be efficiently removed by mixed-mode chromatography, while VHH sometimes triggers truncated variants that can be removed through polishing steps. This kind of insight, based on extensive direct experience from a large number of BsAb projects, can greatly accelerate the development of appropriate analytical control processes.

In particular, the capability of chromatographic techniques to remove various by-products has been intensively investigated, helping to accelerate the development of the BsAb purification process. By relying on a comprehensive suite of techniques, including extensive expertise in chromatography technology and a database of nearly 200 BsAb projects, successful downstream processes can be developed within a markedly reduced timeline. GEN

Sherry Gu, PhD, is executive vice president and CTO at WuXi Biologics. This is an abbreviated version of a longer article that appeared in GEN online in March.

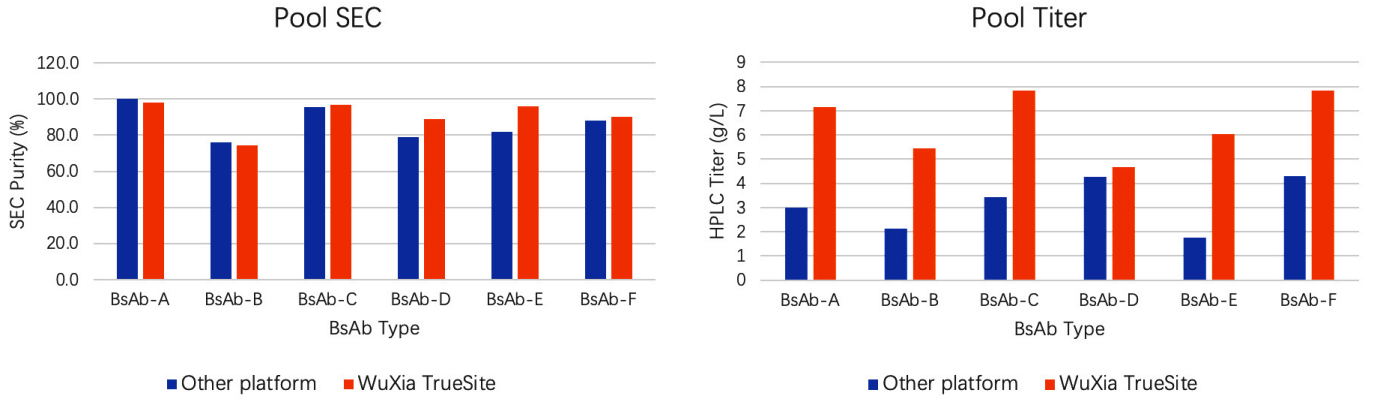


Figure C. Application of the novel WuXia™ TrueSite CHO platform resulted in improved BsAb titer and purity.

Mirna Jarosz, PhD

LIQUIDCELL DX

As CEO, she will lead strategy, operations, and commercialization planning as the company advances its blood based platform for tumor microenvironment profiling. She brings founding stage and scale up experience from Foundation Medicine, 10x Genomics, Ultima Genomics, and Integrated DNA Technologies.

Henning Steinhagen, PhD

SYMERES

As CEO, he will lead Symeres' next phase of growth as the company scales its integrated transatlantic CRDMO platform. He brings more than 25 years of experience across pharma, biotech, and the CRO/CDMO sector, including senior roles at Aptuit, Grünenthal, Sanofi, Bayer, and Lario Therapeutics.

ELKEDONIA has appointed **Pierre d'Epenoux** as independent chairman of their board of directors.

Francisco De La Vega, DSc, has joined **ULTIMA GENOMICS** as vice president of germline genomics and distinguished scientific fellow.

STELLAROMICS has appointed **Veronica Mankinen** as senior vice president of global commercial operations and **John Leamon, PhD**, as senior vice president of product development.

QUANTITATIVE BIOSCIENCES Institute has hired **John A. T. Young, PhD**, as chief strategy officer.

CPTX has appointed **Edward Rebar, PhD**, as its chief scientific officer and **David Maier** as chief business officer.

GC THERAPEUTICS announced **Stefan Irion, MD**, as chief scientific officer.

Mark Altmeyer was elected chairman of the board at **EXCIVA.**

SEER announced **Anthony Bazarko** as chief commercial officer.

PEPTISYSTEMS has appointed **Ole J. Dahlberg** to its board of directors.

EPILEPSYGTX has appointed **Dimitri Kullmann, DPhil**, as chief scientific officer.

EXMOOR PHARMA has appointed **George Fotiades** as chair.

Gregory Esemplare has been appointed chief operating officer of **HARMONYRX**.

CURACELL has appointed **Thomas Jaecklin, MD**, and **Martin Forster, MD, PhD**, to the board of directors.

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Products To Watch

Bio-Based Solvents for High-Performance Liquid Chromatography

MilliporeSigma has introduced a portfolio of bio-based solvents for high-performance liquid chromatography (HPLC), manufactured from renewable feedstocks as drop in alternatives to conventional HPLC grade acetonitrile, methanol, and ethanol. The solvents are designed to match the performance of existing materials and are compatible with established HPLC and LC MS methods, allowing laboratories to use them in routine and regulated analytical workflows. They can be applied in separation and quantification tasks across drug development, manufacturing quality control, environmental monitoring, and diagnostic testing.

MilliporeSigma
www.sigmaaldrich.com

Cryopreservation Buffer for Single-Cell and Multiomics Samples

Waters has introduced the OMICS Guard™ CRYO Preservation Buffer, a cryopreservation solution designed to maintain cellular and molecular integrity for downstream single-cell and multiomics analyses. The buffer supports long term storage of intact cells, whole blood, and tissue in liquid nitrogen and is intended to preserve gene expression, protein epitopes, and chromatin accessibility for later RNA, protein, and chromatin based analyses. It is compatible with the Rhapsody system and is suited for laboratories that need to store and transport samples across sites or time points while maintaining consistency in downstream data quality.

Waters
www.bdbiosciences.com

Ambient Temperature Preservation System for Organoids and Spheroids

Atelerix has launched STORganoid™, an ambient temperature preservation solution designed to store and transport organoids and spheroids without cryopreservation. The system uses the company's hydrogel encapsulation technology to stabilize 3D cell models during extended storage and shipment, helping maintain viability and structural integrity in assay ready formats. By removing the need for cold chain logistics and reducing handling steps, STORganoid supports the distribution and use of complex 3D models in applications such as drug discovery, disease modeling, and personalized medicine.

Atelerix
www.atelerix.co.uk

Thermal Cyclers for Routine PCR Applications

Bio-Rad has launched the PTC Harmony 96 and PTC Harmony Deepwell thermal cyclers, designed for PCR workflows in academic and biopharma laboratories. The instruments provide the same thermal performance as the company's PTC Tempo line in a streamlined format that includes manual lid operation, an intuitive user interface, and connectivity options for protocol management. The systems support applications such as sequencing, cloning, and genotyping.

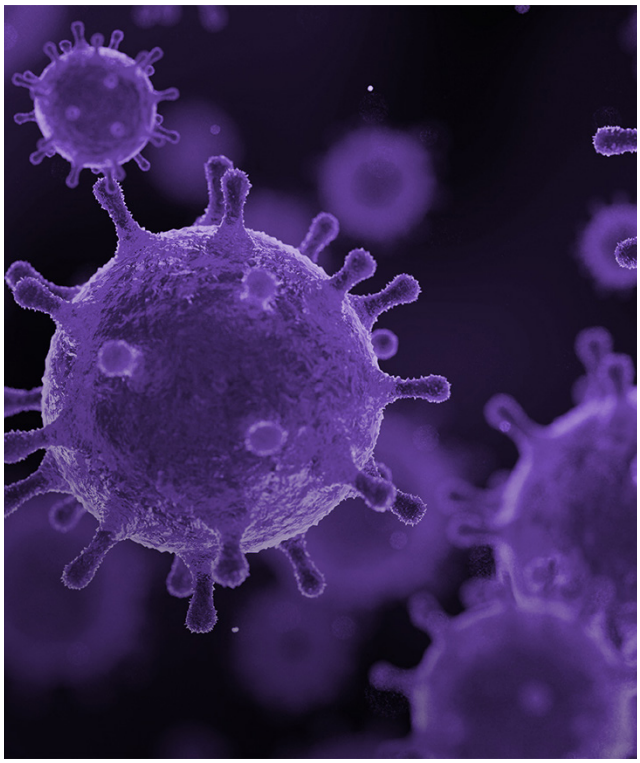
Bio-Rad Laboratories
www.bio-rad.com

Full Range Electronic Pipette for 1–1000 µL Liquid Handling

DeNovix has introduced the Squid™ Full Range Pipette, an electronic pipette designed to cover a 1–1000 µL volume range in a single device. The instrument uses Dynamic Volume Control™, which combines a tip selection mechanism with motor controlled dispensing to support two operating modes for 200 µL and 1000 µL tips. This allows the pipette to perform tasks typically requiring multiple single channel pipettes while maintaining ISO 8655 compliant performance across its full range. The Squid is compatible with universal pipette tips, and DeNovix also offers tips optimized for the device.

DeNovix
www.denovix.com

RT qPCR and qPCR Kits for Molecular Diagnostics Assay Development



Watchmaker Genomics has expanded its molecular diagnostics portfolio with the launch of Stellar RT qPCR and qPCR Kits, designed for assay developers working across PCR and isothermal modalities. The kits incorporate the company's engineered StellarTaq™ DNA Polymerase and StellarScript® HT+ Reverse Transcriptase to support rapid cycling and amplification from crude or minimally processed samples. They are intended for use in applications requiring fast turnaround and inhibitor tolerant performance, including point of care and field deployable testing. The kits complement Watchmaker's recombinase polymerase amplification (RPA) enzyme suite.

Watchmaker Genomics
www.watchmakergenomics.com

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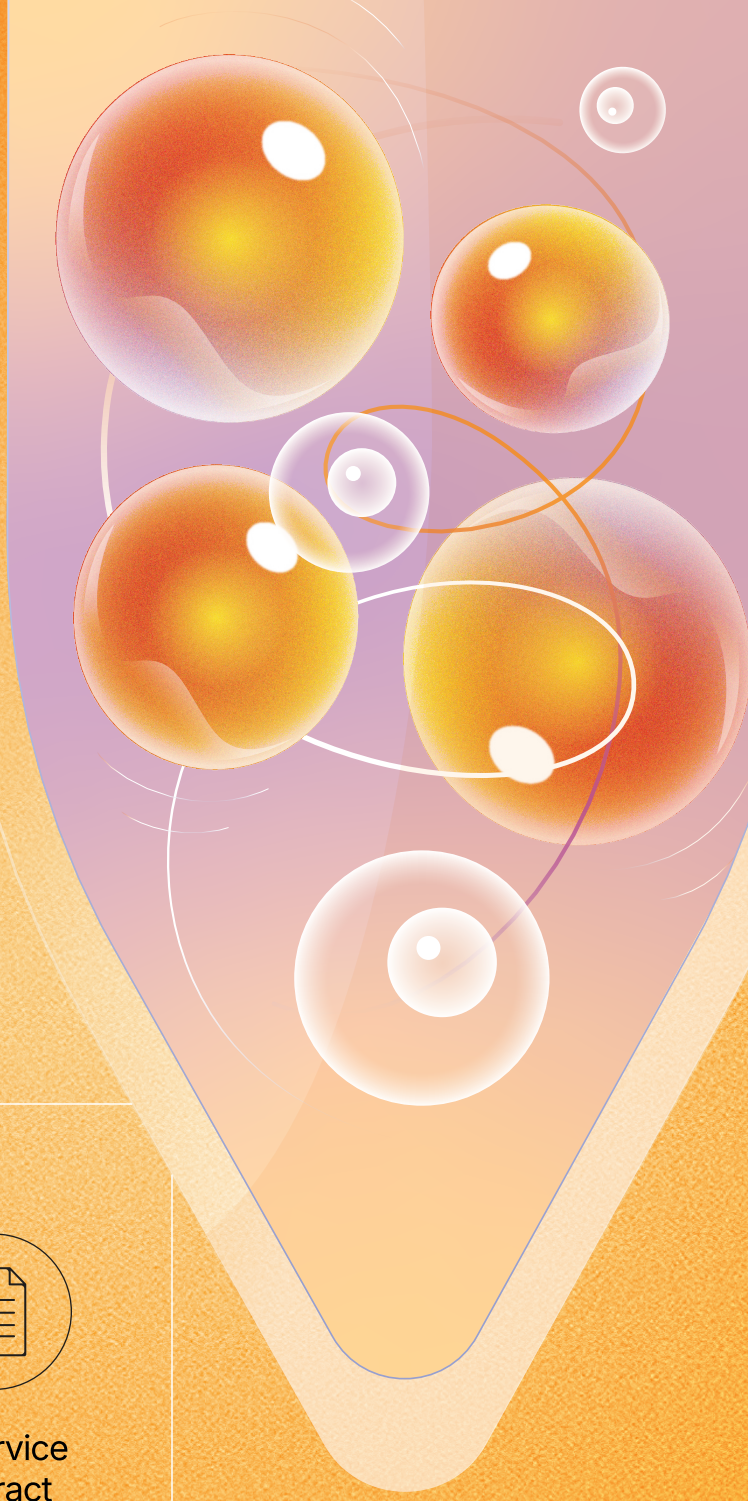

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